RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF)
Randomized Clinical Trial

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1 PROTOCOL SYNOPSIS

Protocol Title:	RENal hemodialysis patients Allocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF) Randomized Clinical Trial
Study Sponsor:	Christopher B. Granger, MD
Number of Sites:	Approximately 65 sites
Research Hypothesis:	Treatment with apixaban causes less major or clinically relevant non-major bleeding than warfarin in patients with end-stage renal disease (ESRD) on hemodialysis with non-valvular atrial fibrillation (NVAF), meaning atrial fibrillation without moderate or severe mitral stenosis.
Study Schema: Drugs / Doses / Length of Treatment)	Open label apixaban 5mg BID (or apixaban 2.5mg BID in patients ≥ 80 years of age and/or ≤ 60 kg) vs. adjusted dose warfarin. Duration of treatment will be a maximum of 15 months, and the target is a mean follow-up of approximately 12 months with the last patient enrolled into the trial having a minimum of 6 months of follow-up.
Study Objectives:	**Primary objective:** Assess the safety of apixaban versus warfarin with respect to major bleeding or clinically relevant non-major bleeding in patients with ESRD on hemodialysis and NVAF **Secondary objectives:** Evaluate stroke and systemic embolism event rates with warfarin and apixaban in patients with NVAF and ESRD on hemodialysis. Evaluate mortality rates with warfarin and apixaban in patients with NVAF and ESRD on hemodialysis. Evaluate persistence (meaning the duration of time from initiation to discontinuation of therapy) of and adherence (meaning the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen) to warfarin and apixaban in patients with NVAF and ESRD on hemodialysis. Evaluate the pharmacokinetics and pharmacodynamics of apixaban in ESRD NVAF patients on hemodialysis.

Study Design:	Prospective, randomized, open-label, blinded end-point evaluation trial (PROBE). Patients with NVAF, ESRD, and a CHA2DS2-VASc score of 2 or greater will be randomized in a 1:1 fashion to apixaban or warfarin. The primary outcome is International Society of Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major bleeding, as defined by a central blinded-clinical events adjudication process. A total of approximately 230 patients (randomized 1:1 in the apixaban and warfarin arms) will be enrolled at approximately 65 sites across the Unites States. Duration of treatment will be a maximum of 15 months, and the target is a mean follow-up of approximately 12 months with the last patient enrolled into the trial having a minimum of 6 months of follow-up.
Accrual Goal: (Total number of patients)	Approximately 230 patients
Pharmacokinetics/ Pharmacodynamics (PK/PD)	For patients enrolled using versions 13 or earlier of the protocol, at Day 1 visit, blood samples were collected for PK on all patients randomized to apixaban. A subset of no more than 50 patients randomized to apixaban had additional PK/PD samples collected at Day 3 visit and at Month 1 visit. Samples were drawn at the start of the hemodialysis session and at the end of the hemodialysis session. For patients enrolled under version 14 of the protocol, no PK/PD samples will be collected.
Inclusion Criteria:	1. Males and Females, age at least 18 years, or the local age of consent, whichever is greater. 2. Patients will be defined as having qualifying AF, if they meet any of the following criteria: a. AF on ECG at enrollment or b. two or more reports of AF from separate monitoring events at least 2 weeks apart (report of ECG, single lead rhythm strip such as AliveCor, inpatient telemetry, Holter monitor, event monitor, implantable loop recorder, pacemaker, or implantable cardioverter-defibrillator), or c. 1 report of AF (report of ECG, single lead rhythm strip such as AliveCor, inpatient telemetry, Holter monitor, event monitor, implantable loop recorder, pacemaker, or implantable cardioverter-defibrillator) and being treated with

	oral anticoagulation for stroke prevention for atrial fibrillation at enrollment, or d. 1 report of AF (report of ECG, single lead rhythm strip such as AliveCor, inpatient telemetry, Holter monitor, event monitor, implantable loop recorder, pacemaker, or implantable cardioverter-defibrillator) and any mention in the medical record of a second episode of AF, or e. history of cardioversion for AF and any mention in the medical record of a second episode of AF or being treated with oral anticoagulation for stroke prevention for atrial fibrillation at enrollment. 3. CHA2DS2-VASc score ≥ 2. 4. End-stage renal disease treated with hemodialysis for ≥ 3 months. 5. Considered by the treating physician(s) to be candidates for oral anticoagulation (for example the patient does not have a reversible cause for AF) 6. If of childbearing potential, be willing to avoid pregnancy during the study.
Exclusion Criteria:	1. Not considered by the treating physician(s) to be candidates for oral anticoagulation (for example, hemoglobin < 8.5g/dL, history of intracranial hemorrhage, active bleeding, recent gastrointestinal bleed or retroperitoneal bleed, severe hepatic impairment, or anaphylactic reaction to apixaban) 2. Moderate or severe mitral stenosis 3. Conditions other than NVAF that require anticoagulation such as mechanical prosthetic valve, deep venous thrombosis, or pulmonary embolism 4. Need for aspirin at a dose > 100 mg a day or need for aspirin in combination with P2Y12 antagonist therapy (for example clopidogrel, prasugrel, or ticagrelor) 5. Life expectancy < 3 months 6. Anticipated kidney transplant within the next 3 months 7. Prisoners or others who are involuntarily incarcerated or detained 8. Pregnant, breastfeeding, or considering pregnancy. 9. Participation in a clinical trial of an unapproved, experimental treatment within the past 30 days

Criteria for Evaluation: (Efficacy, safety, stopping rules, etc.)	The primary safety outcome is ISTH major bleeding or clinically relevant non-major bleeding
Statistics:	The analytic plan will be exploratory, and based on the observed point estimate (hazard ratio) and its 95% CIs for the comparison of the primary endpoint for the apixaban arm versus the warfarin arm. In addition, Kaplan-Meier cumulative risk curves will be constructed and a log-rank test will be used.

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3 INTRODUCTION

Impaired kidney function and atrial fibrillation (AF) commonly occur together with approximately 13% of patients on hemodialysis in the United States having AF.[1] Impaired kidney function is common in the elderly, who are also at the highest risk for AF. Impaired kidney function is an independent predictor both of stroke and of bleeding in patients with AF. There is a 1.5-fold increased risk of stroke and 2-fold increased risk of bleeding in patients with end-stage renal disease (ESRD) compared to patients without ESRD.[2] Among patients on hemodialysis, the risks of gastrointestinal and other serious bleeding events, ESRD-related dietary restrictions, frailty and a high risk of falls, polypharmacy, and the need for repeated cannulation of arteriovenous fistulas and grafts vascular access type may influence decisions regarding the use of anticoagulation. In addition to the usual risks associated with anticoagulation in general, the use of warfarin in particular is associated with additional risks unrelated to bleeding, related to inhibition of other vitamin K dependent pathways, including those related to dystrophic calcification. Warfarin has consistently been identified as a risk factor in the development of calcific uremic arteriolopathy ("calciphylaxis"), a rare, but life-threatening complication, emblematic of accelerated medial vascular calcification.[3, 4]

There is uncertainty as to the risk-benefit balance of warfarin for patients on hemodialysis with AF. [2, 5-7] Patients receiving hemodialysis may have different relative benefits given different pro- and anti-thrombotic factors related to ESRD and different risks related to hemostasis defects, gastrointestinal and vascular access bleeding. In any case, it is clear that patients with advance kidney disease are at high risk for stroke. A Danish registry study showed that warfarin use was associated with lower risk of stroke in ESRD and that aspirin was not associated with lower risk of stroke in this population.[2] These findings are consistent with a benefit from warfarin and lack of substantial benefit from aspirin. There is striking geographic variability in the treatment of AF in patients with ESRD, with only about fewer than half of patients being treated with warfarin in the United States.[5] Many experts have suggested that therapy should be individualized, such that patients at high risk for stroke and without high bleeding risk should be treated with oral anticoagulation. In reality, this may be difficult to do, since many of the same factors predict risk of bleeding and thrombosis.

Apixaban is an oral factor Xa inhibitor that is an anticoagulant with superior efficacy for reducing stroke or systemic embolism in NVAF (non-valvular AF, meaning atrial fibrillation without moderate or severe mitral stenosis) compared to warfarin and with significantly less major bleeding than warfarin when used in the general AF population. It is also significantly more efficacious than aspirin, with a non-statistical slightly higher rate of major bleeding and similar risk of intracranial hemorrhage.[8, 9] Apixaban has been labeled by the FDA as suitable for use in patients with impaired kidney function (including those receiving dialysis), although this designation was based on pharmacokinetic and pharmacodynamics data without clinical outcomes data.[10] Dabigatran or rivaroxaban, which are not labeled as suitable for use in ESRD, are being

used in nearly 6% of ESRD patients receiving anticoagulation, and dabigatran and rivaroxaban relative to warfarin are associated with higher rates of hospitalization or death due to bleeding in this population.[11] Patients with advanced kidney disease may obtain similar or greater benefit from optimally dosed non-vitamin K antagonist oral anticoagulants (NOAC), as warfarin.[12] There is a need for randomized clinical trials of novel oral anticoagulants in the population of patients with AF and ESRD on hemodialysis.[7, 13, 14]

3.1 Overall Risk/Benefit Assessment

Patients with AF and ESRD are at high risk of stroke, and warfarin has been proven to be very effective at stroke prevention in the general population.[15] Warfarin is currently a standard treatment for stroke prevention in patients with ESRD. However, warfarin has not been studied in a randomized manner in AF patients with ESRD, and warfarin may have limitations in population with ESRD that are different from the population without ESRD. Warfarin is associated with calciphylaxis, which carries a high mortality.[3, 4] Patients with ESRD are at high risk of bleeding, and when treated with warfarin, ESRD may be at higher risk of serious bleeding such as intracranial hemorrhage relative to non-ESRD patients.[16]

All currently marketed NOACs have some component of renal clearance, and there has been concern with using these medications in patients with ESRD. However, there is an unmet need for alternatives to warfarin for reducing the risk of stroke or systemic embolism in NVAF patients with ESRD. Based on pharmacokinetics and pharmacodynamics, apixaban may be safe in the ESRD population.[10] In the ARISTOLE trial, patients with impaired kidney function (estimated creatinine clearance 25 to 50 ml/min, roughly corresponding to stage 3b/4a CKD) had a more pronounced relative reduction in major bleeding versus warfarin than patients with higher creatinine clearance (HR 0.50, 95% CI 0.38-0.66, interaction $p = 0.005$.[17] Apixaban may result in less intracranial hemorrhage than warfarin in the ESRD patient population, similar to the general population.[9] There is also evidence that warfarin may become less effective at preventing ischemic stroke, compared to NOACs, as kidney function decreases.[26]

3.2 Research Hypothesis

Treatment with apixaban causes less major or clinically relevant non-major bleeding than warfarin in patients with end-stage renal disease (ESRD) on hemodialysis with non-valvular atrial fibrillation (NVAF), meaning atrial fibrillation without moderate or severe mitral stenosis.

3.3 Study Rationale

There were 450,000 patients receiving maintenance dialysis in the US, as of 2012, which has increased by 57%, since the year 2000.[18] The prevalence of NVAF is higher in the dialysis population than in the general population[1] and the risk of stroke is also higher in the dialysis population.[2] There is an important need to study and identify strategies to reduce stroke risk in patients on hemodialysis with NVAF. Warfarin is highly effective in reducing the risk of stroke

by 66% in the overall population of patients with NVAF.[15] However, warfarin use has never been studied in patients on hemodialysis with NVAF. Based on conflicting data from observational studies regarding the risks and benefits of warfarin for stroke prevention in patients on hemodialysis with NVAF,[1, 2, 5, 16, 19] the 2011 statement from Kidney Disease: Improving Global Outcomes (KDIGO) did not advise warfarin for stroke prevention in patients on hemodialysis with NVAF, and these statements specifically highlighted the need for clinical trials addressing this issue.[13]

The RENAL-AF (RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation) Trial is a prospective, randomized, open-label, blinded end-point evaluation (PROBE) study of apixaban versus warfarin for reduction of the composite of major bleeding or clinically relevant non-major bleeding in patients with NVAF and ESRD on hemodialysis. The lower rates of bleeding with apixaban relative to warfarin, especially intracranial hemorrhage, may make apixaban safer than warfarin for the reduction of the risk of stroke or systemic embolism in patients with ESRD and NVAF. This randomized clinical trial will also evaluate differences in stroke or systemic embolism among NVAF patients with ESRD on hemodialysis who are deemed candidates for anticoagulation by their treating physicians and will be randomly assigned to apixaban versus warfarin. There have been no prospective, randomized clinical trials investigating reducing the risk of stroke or systemic embolism in patients with ESRD and NVAF.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective is to assess the safety of apixaban versus warfarin regarding major bleeding or clinically relevant non-major bleeding events in patients with NVAF and ESRD on hemodialysis.

4.2 Secondary Objectives

The secondary objectives are to:

1. Evaluate stroke and systemic embolism event rates with warfarin and apixaban in patients with NVAF and ESRD on hemodialysis.
2. Evaluate mortality rates with warfarin and apixaban in patients with NVAF and ESRD on hemodialysis.
3. Evaluate persistence (meaning the duration of time from initiation to discontinuation of therapy) of and adherence (meaning the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen) to warfarin and apixaban in patients with NVAF and ESRD on hemodialysis.
4. Evaluate the pharmacokinetics and pharmacodynamics of apixaban in ESRD NVAF patients on hemodialysis.

4.3 Other Objectives

Other objectives will include analysis of outcomes and treatment effect according to levels of cardiovascular biomarkers at baseline.

5 ETHICAL CONSIDERATIONS

5.1 Good Research Practice

This trial will be conducted in compliance with this protocol, Good Clinical Practice guidelines (e.g. ICH E6: Good Clinical Practice), and applicable regulatory requirements from the United States Code of Federal Regulations including 21 CFR parts 312 (Investigational New Drug [IND]), 50 (Protection of Human Subjects, 56 (institutional review board [IRB]), and 11 (electronic records and signatures).

All individuals responsible for the design and/or conduct of this study are to have completed and documented human subjects' protection training prior to participation.

The site principal investigator shall ensure that personnel involved in the conduct of this study are qualified by education, training, and experience to perform their respective tasks. The site principal investigator has ultimate responsibility for trial conduct at the site.

5.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, patient recruitment materials/process (e.g., advertisements), and any other written information to be provided to prospective patients. The investigator or sponsor should also provide the IRB/IEC with a copy of the product labeling information to be provided to prospective patients, and any updates.

The investigator should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

5.3 Informed Consent

Investigators must ensure that patients are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Before any study procedures are performed, potential patients will have the outline of the study described to them, and they will be given a written informed consent document to read. If they consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel. Any patient who signs the consent form will be considered a "screened" patient.

6 INVESTIGATIONAL PLAN

6.1 Study Design and Duration

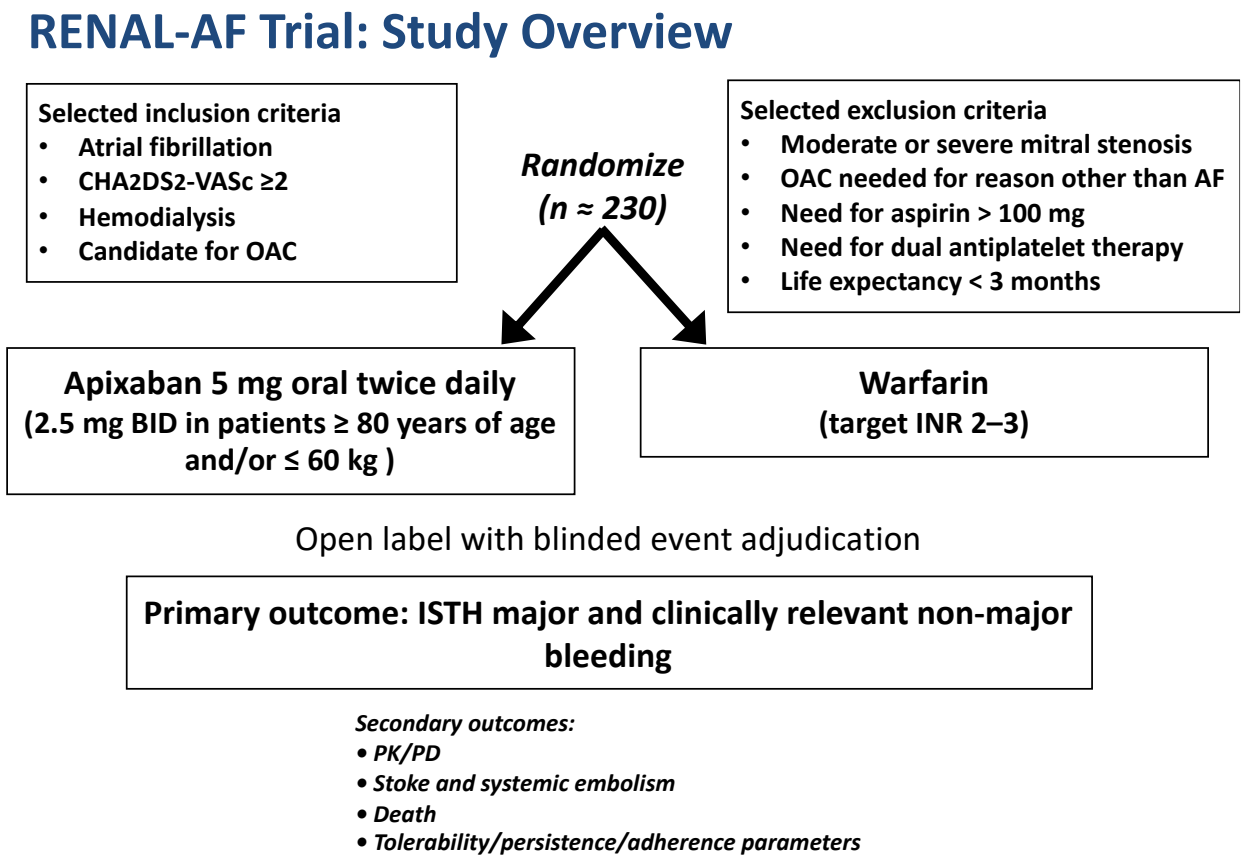
The study is a prospective, randomized, open-label, blinded end-point evaluation trial. Patients with NVAF, ESRD, and a CHA2DS2-VASc of 2 or more (Appendix 1) will be randomized in a 1:1 fashion to apixaban or warfarin. The primary outcome is International Society of Thrombosis and Haemostasis (ISTH) major bleeding and clinically relevant non-major bleeding, adjudicated by a central clinical events process.

A total of approximately 230 patients (randomized 1:1 to apixaban and warfarin) will be enrolled at approximately 65 sites across the Unites States. The maximum follow-up time will be approximately15 months, and the target follow-up time will be a mean of 12 months with the last patient enrolled into the trial having a minimum of 6 months of follow-up..

Pharmacokinetics and pharmacodynamics analyses will be performed in a subset of patients to determine apixaban concentrations. For patients enrolled using versions 13 or earlier of the protocol, at Day 1 visit, blood samples were collected for PK on all patients randomized to apixaban. A subset of no more than 50 patients randomized to apixaban had additional PK/PD samples collected at Day 3 visit and at Month 1 visit. Samples were be drawn at the start of the hemodialysis session and at the end of the hemodialysis session. For patients enrolled using version 14 of the protocol, no PK/PD samples will be collected.

The schematic provided in Figure 6-1 summarizes the study design.

Figure 6-1 Study Schematic



6.2 Study Population & Eligibility Criteria

For entry into the study, the following criteria MUST be met. Entry waivers will not be granted.

6.2.1 Inclusion Criteria

1. Males and Females, age at least 18 years, or the local age of consent, whichever is greater.
2. Patients will be defined as having qualify AF, if they meet any of the following criteria:
    a. AF on ECG at enrollment,
    b. two or more reports of AF from separate monitoring events at least 2 weeks apart (report of ECG, single lead rhythm strip such as AliveCor, inpatient telemetry, Holter monitor, event monitor, implantable loop recorder, pacemaker, or implantable cardioverter-defibrillator),

c. 1 report of AF (report of ECG, single lead rhythm strip such as AliveCor, inpatient telemetry, Holter monitor, event monitor, implantable loop recorder, pacemaker, or implantable cardioverter-defibrillator) and being treated with oral anticoagulation for stroke prevention for atrial fibrillation at enrollment,
d. 1 report of AF (report of ECG, single lead rhythm strip such as AliveCor, inpatient telemetry, Holter monitor, event monitor, implantable loop recorder, pacemaker, or implantable cardioverter-defibrillator) and any mention in the medical record of a second episode of AF, or
e. history of cardioversion for AF and any mention in the medical record of a second episode of AF or being treated with oral anticoagulation for stroke prevention for atrial fibrillation at enrollment

3. CHA2DS2-VASc score of ≥ 2.
4. End-stage renal disease treated with hemodialysis for at least 3 months.
5. Considered by the treating physician(s) to be candidate for oral anticoagulation. (i.e. patient does not have a reversible cause for AF) [OAC treatment naïve or subjects currently receiving OAC are eligible].
6. If of childbearing potential, be willing to avoid pregnancy during the study.

6.2.2 Exclusion Criteria

1. Not considered by the treating physician(s) to be candidates for oral anticoagulation (for example, hemoglobin < 8.5g/dL, history of intracranial hemorrhage, active bleeding, recent gastrointestinal bleed or retroperitoneal bleed, severe hepatic impairment, or anaphylactic reaction to apixaban)
2. Moderate or severe mitral stenosis
3. Conditions other than NVAF that require anticoagulation such as mechanical prosthetic valve, deep venous thrombosis, or pulmonary embolism
4. Need for aspirin at a dose > 100 mg a day or need for aspirin in combination with P2Y12 antagonist therapy (for example clopidogrel, prasugrel, or ticagrelor)
5. Life expectancy < 3 months
6. Anticipated kidney transplant within the next 3 months
7. Prisoners or others who are involuntarily incarcerated or detained
8. Pregnant, breastfeeding, or considering pregnancy.
9. Participation in a clinical trial of an unapproved, experimental treatment within the past 30 days

6.2.3 Women of Childbearing Potential & Breastfeeding Women

For purposes of this protocol, the terminology “women of childbearing potential (WOCBP)” is defined as any female who has experienced menarche and who has not undergone

surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

- Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40mIU/ml at any time during the washout period, the woman can be considered postmenopausal:
    - 1 week minimum for vaginal hormonal products (rings, creams, gels)
    - 4 week minimum for transdermal products
    - 8 week minimum for oral products
    - Other parenteral products may require washout periods as long as 6 months.

Women of childbearing potential (WOCBP) must have a negative urine (use serum if patient is anuric) within 24 hours prior to randomization to apixaban or warfarin. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with apixaban or warfarin (s) plus 5 half-lives of warfarin (8 days) or apixaban (3 days) plus 30 days (duration of ovulatory cycle) for a total of 38 days for warfarin and 33 days for apixaban post-treatment completion.

Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) YY plus 5 half-lives of warfarin (8 days) or apixaban (3 days) plus 90 days (duration of sperm turnover) for a total of 98 days for warfarin and 93 days for apixaban post-treatment completion.

Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However WOCBP must still undergo pregnancy testing.

Investigators shall counsel WOCBP and male patients who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male patients who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. At a minimum, patients must agree to the use of one method of highly effective contraception as listed below:

- Male condoms with spermicide
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy

- Complete Abstinence
    - Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence.
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP patient or male patient's WOCBP partner. . Female partners of male patients participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug.

  Women who are breastfeeding are not allowed to participate in this study.

6.2.4 Discontinuation of Patients from Treatment

Patients may discontinue study drug for any of the following reasons:

- Patient's decision to stop study treatment for any reason. Should a patient decide to stop study treatment, we will request he or she remain in follow-up, and we will follow them through medical records and/or death registries.
- Any clinical adverse event, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient.
- Pregnancy
    - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (e.g. missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
    - The investigator must immediately notify the sponsor if a study patient becomes pregnant.
    - Male patients whose partners are WOCBP should contact the investigator or study staff immediately if a pregnancy in the female partner is suspected or confirmed. Institutional policy and local regulations should determine the appropriate steps.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness.
- Any other study specific reasons.

All patients who discontinue should comply with protocol-specified follow-up procedures outlined in Section 8. Guidance will be provided in the Study Manual on how to transition to standard of care anticoagulation therapy at the end of the trial.

6.2.5 Transition to Standard of Care Anticoagulation Therapy at End of Trial

Prior to the day of the final dose of study drug, Principal Investigators should discuss with their patients, and with the patients' treating physicians, whether to begin open-label warfarin at a dose judged appropriate by the treating physician; e.g. based on the clinical profile of the subject including age, dry body weight or hemodialysis target body weight, creatinine clearance, concomitant therapies or other clinical conditions. A resource that can be used to choose initial dose is www.warfarindosing.org.

For those patients that will transition to warfarin from apixaban, the day following the final study-mandated apixaban dose, the apixaban dose will be decreased by half (from 5mg BID to 2.5mg BID) and warfarin initiated; the patient will take 2.5mg apixaban BID in addition to warfarin. This "combination" therapy will continue until an INR of at least 2.0 has been obtained. INR should be measured two to three days after the first warfarin dose. An appropriate adjustment to the open-label warfarin dose should be made with the suggestion to use an algorithm like that found in the study (protocol section 7.4.3) or per local standards. Once there is an INR value of 2.0 or greater, the apixaban should be stopped, and the warfarin dosing should continue.

7 TREATMENTS

7.1 Study Treatment: Apixaban

7.1.1 Identification

Product descriptions, packaging/storage, and other specifications of the study drugs in the RENAL-AF study are summarized in Table 7-1.

Table 7-1 Study Drugs for RENAL-AF

Product Description / Class and Dosage Form	Potency	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Apixaban film coated tablets	5mg	Open label	Commercial marketed presentation	As per label
Apixaban film coated tablets	2.5mg	Open label	Commercial marketed presentation	As per label
Warfarin sodium	Per provider	Open label	Commercial marketed presentation	As per label

7.1.2 Handling and Dispensing

Apixaban should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study patients and only from official study sites by authorized personnel, as dictated by local regulations.

If concerns regarding the quality or appearance of apixaban arise, do not dispense the investigational product, and contact the sponsor immediately.

7.1.3 Drug Destruction

Since apixaban and warfarin are both commercially available, study drug will be destroyed according to the local institution requirements.

7.2 Drug Ordering and Accountability

Apixaban will be supplied to the investigator as part of the study materials. Warfarin will be obtained by the patients from a retail pharmacy with a prescription from their prescribing provider, but the costs of the warfarin prescriptions will be reimbursed by the RENAL-AF trial.

7.2.1 Initial Orders

Initial apixaban supplies will be provided upon site activation per sponsor's SOPs. Supplies will be shipped by the sponsor's specified vendor. Additional details will be provided in the study reference manual.

7.2.2 Re-Supply

Sites should request resupply of apixaban to the sponsor's specified vendor. Enough lead time should be given to ensure apixaban is on site in advance of the study visit. Additional details will be provided in the study reference manual.

7.2.3 Accountability

Apixaban documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug receipt, dispensation and administration records, and destruction records.

7.3 Method of Assigning Patients to a Treatment

Each patient will be assigned a unique sequential patient number. Each patient that meets the inclusion and exclusion criteria will be randomly assigned in a 1:1 manner to apixaban or dose adjusted warfarin with an INR goal of 2.0-3.0. Randomization will be stratified by investigative site and prior warfarin status (experienced versus naïve). Patients will be considered warfarin naïve if they have never previously been on warfarin or if they have started warfarin within the last 30 days. Patient randomization will occur within the electronic data capture (EDC) system.

Patients on warfarin at baseline will be randomized to either the apixaban or warfarin arm. If the patient is randomized to the warfarin arm, he or she will continue on dose adjusted warfarin without any transition in oral anticoagulation regimen. If the warfarin patient is randomized to apixaban, warfarin will be held, and apixaban will be started once the patient's INR value is < 2.0.

For patients on a NOAC at baseline, he or she will be randomized to either the apixaban or warfarin arm. For those patients randomized to apixaban, the patient should start apixaban at the time of their next regularly scheduled dose of the baseline NOAC. For those patients randomized to warfarin, he or she should be started on warfarin in addition to the baseline oral anticoagulant, with the recommendation that the NOAC be reduced to half the full dose (ie, apixaban 2.5 mg bid, dabigatran 75 mg bid, rivaroxaban 10 mg q d, edoxaban 30 mg q d), with plans to stop the baseline oral anticoagulant (and continue warfarin) once the INR level reaches 2.0. When deciding whether to use this half-dose NOAC "bridge" strategy, take into account thrombotic risk, for example based on history of prior stroke.

7.4 Selection and Timing of Dose for Each Patient

If a dose of apixaban is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and then continue with twice daily administration as before. The dose should not be doubled to make up for a missed dose.

Apixaban can be taken with or without food.

7.4.1 Apixaban Dose Modifications

In patients with at least 1 of the following characteristics: age ≥ 80 years or dry body weight/hemodialysis target body weight ≤ 60 kg, the recommended dose of apixaban is 2.5 mg twice daily, and patients should receive the 2.5 mg dose at any point during the trial at which they have met one of these characteristics (for example, a patient with an age of 79 years at enrollment and body weight/hemodialysis target body weight > 60kg would receive the 5 mg dose at enrollment but should receive the 2.5 mg dose around their 80th birthday). If a study patient is taking apixaban 5 mg twice daily and is experiencing minor bleeding, the site investigator will be able to contact the study leadership to discuss temporary dose adjustments to 2.5 mg twice daily. The dates and reason for all dose adjustments to 2.5 mg twice daily must be recorded. Patients taking strong dual inhibitors of CYP3A4/P-gp (examples include ketoconazole, itraconazole, ritonavir, and clarithromycin) should have their dose adjusted to 2.5 mg twice daily based on the United States package insert. Patients taking dual inhibitors of CYP3A4/P-gp that are not strong inhibitors should consider dose reduction to 2.5 mg twice daily. If patients are already taking the 2.5 mg dose apixaban, avoid co-administration of these medications. Cardiologists and nephrologists from the study leadership will be available to discuss dosing and advise about potential apixaban dosing adjustments.

7.4.2 Temporary Discontinuation of Apixaban

Discontinuing anticoagulants, including apixaban, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided, and if anticoagulation with apixaban must be temporarily discontinued, therapy should be restarted as soon as possible. See Section 7.6.2 for additional details.

7.4.3 Warfarin Dose Modifications

The patient's prescribing provider (any provider caring for the patient with primary responsibility for warfarin management, including providers from a warfarin clinic or providers other than the study investigator) in this open label study will select the warfarin dose. The goal INR will be 2.0-3.0, and the patient's provider should monitor the INR level and adjust the dose of warfarin accordingly. The frequency of INR measurements are at the discretion of the prescribing provider; however, we recommend that INR values are drawn at least once a month and more frequently at the time of warfarin initiation or around INR values out of the therapeutic range. All INR values will be recorded on the eCRF.

Warfarin dosing will be daily and patients will be instructed to follow all prescribing instructions. Sites that are working with a clinic that have a warfarin dosing algorithm should continue to use that algorithm for this study. For providers managing warfarin without a treatment algorithm, the treatment algorithm from the ARISTOTLE trial is listed in Table 7-2 and may be used as guidance for dose adjustment of warfarin in order to maximize the time in the therapeutic range (2.0-3.0). Prescribing providers are responsible for initial dose selection and any dose adjustments. Additional resources can be located at:

- http://www.careinternet.net/caregiver/warfarin.php
- www.warfarindosing.org

Table 7-2 Warfarin Dosing Algorithm from the ARISTOTLE Trial as Optional Guidance for Warfarin Management

INR Value	Action
> 10.0	Stop warfarin. Contact patient for examination.
7.0-10.0	Stop warfarin for 2 days; decrease weekly dosage by 25% or by 1 mg/day for next week (7 mg total); repeat lab assessments in 1 week.
4.5-7.0	Decrease weekly dosage by 15% or by 1 mg/day for 5 days of next week (5 mg total); repeat lab assessments in 1 week.
3.0-4.5	Decrease weekly dosage by 10% or by 1 mg/day for 3 days of next week (3 mg total); repeat lab assessments in 1 week.
2.0-3.0	No change.
1.5-1.9	Increase weekly dosage by 10% or by 1 mg/day for 3 days of next week (3 mg total); repeat lab assessments in 1 week
< 1.5	Increase weekly dosage by 15% or by 1 mg/day for 5 days of next week (5 mg total); repeat lab assessments in 1 week

See Section 7.6.2 for instructions regarding temporary discontinuation for warfarin for surgeries or procedures.

7.5 Blinding/Unblinding

Not applicable as study is not blinded to study staff or patients.

7.6 Concomitant Treatments

7.6.1 Prohibited and/or Restricted Treatments

Co-administration of apixaban is not recommended with drugs that increase the risk of bleeding (e.g., other anticoagulants, heparin (excluding any heparin that might be used for tunneled hemodialysis catheter locks), thrombolytic agents).

Heparin during hemodialysis should be minimized in all patients (randomized to apixaban or warfarin). If the investigator believes that a patient in the study has an indication for and would benefit from heparin with hemodialysis, we advise that a heparin bolus of no more than 5,000 units

should be given at the onset of hemodialysis. If heparin is co-administered, the reason and the dose must be documented within the eCRF. In place of heparin, the circuits should be flushed every hour during the hemodialysis session. If a patient has thrombosis of the extracorporeal circuit when heparin is not used, then the patient should receive heparin in the priming solution for the extracorporeal circuit during the remaining dialysis sessions, while the patient is enrolled in the trial. As above, the reason heparin was administered and the dose must be documented within the eCRF.

7.6.2 Other Restrictions and Precautions

Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping apixaban and prior to the intervention is not generally required. Apixaban should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. If surgery or invasive procedures cannot be delayed, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding. Patients will be excluded from the trial if there is a need for aspirin at a dose > 100 mg or aspirin in combination with P2Y12 antagonist therapy (for example clopidogrel, prasugrel, or ticagrelor). Patients may be included if they have an indication for P2Y12 antagonist therapy without the concomitant use of aspirin (for example, in the case of an aspirin allergy).

Warfarin should be held 3 to 5 days (depending on the patient's INR value) prior to the surgery or invasive procedure with the goal of having the patient's INR value < 1.7 at the time of the surgery or procedure, depending on the bleeding risk of the procedure or surgery. For surgery or procedures where serious bleeding risk is high, like many neurosurgeries, the INR should return to normal before proceeding.

7.7 Treatment Adherence and Persistence

Persistence is defined as the duration of time from initiation to discontinuation of therapy, and this will be measured for apixaban and warfarin. Adherence is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen. Time in therapeutic range (TTR) will be used to monitor treatment adherence among patients on warfarin. Pill counts will be used to monitor treatment adherence among patients on apixaban.

Additionally, a single-item self-reported medication adherence question that has been associated with hospitalization and death in cardiovascular patients will be asked of all patients in order to provide a direct comparison between the adherence of the apixaban and warfarin patients:

"Out of the past 7 days, did you miss a dose of your blood thinner?".[20] A second self-reported adherence question will also be asked: "Over the last 30 days, how often have you taken your blood thinner: less than 20% (5 days or fewer), 20-80% (6 days to 23 days), or greater than 80% (24 days or more) of the time?".[21] This data will be collected at the quarterly visits.

8 STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures will be recorded within the clinical database. A schedule of study procedures can be located in Appendix 2. All laboratory assessments will be performed according to the standard of care schedule for the patient.

8.1 Screening & Randomization

If needed, screening and randomization can occur on separate days (for example, if additional documentation needs to be collected between screening and randomization). However, once a patient is randomized within the system, the Day 1 visit and start of drug should occur within 3 days or as soon as the INR value is < 2.0 in the case of patients on warfarin at the time of enrollment, who were randomized to apixaban (Appendix 3). Investigator or designee will:

- Obtain written patient informed consent
- Review inclusion and exclusion criteria to confirm patient eligibility for randomization
- Review relevant medical history and all concomitant medications
- Obtain vital signs
- Measure height and dry body weight or hemodialysis target body weight
- Perform ECG, perform a single lead rhythm strip such as AliveCor, or obtain an ECG within the last 30 days prior to enrollment
- Obtain laboratory samples (CBC, BMP, INR), or provide results from most recent laboratory evaluations if within the last 30 days prior to enrollment
- Collect urine pregnancy test (for those women of childbearing potential). If patient is anuric a serum pregnancy test may be performed.
- Provide pregnancy prevention counseling as outlined in Section 6.2.3
- If patient is eligible, randomize patient via the Electronic Data Capture (EDC) system
    - Detailed instructions can be found in study reference manual
- Dispense medication or prescription and provide instructions (Appendix 3)
    - If the patient is randomized to apixaban, he or she will receive a 3-month supply of study drug at the time of randomization.

- If the patient is randomized to warfarin, the patient's provider (any provider caring for the patient with primary responsibility for warfarin management, including providers from a warfarin clinic or providers other than the study investigator) will prescribe warfarin and the patient will fill the prescription at a commercial pharmacy. Warfarin dose should be managed to ensure a target INR value of 2.0-3.0.
- For patients randomized to apixaban, when it is feasible based on the timing of hemodialysis, instruct the patient to take morning dose of apixaban at least 2 hours prior to the scheduled hemodialysis time for the Day 1 visit. If the timing of hemodialysis (early morning session) makes it unfeasible to take apixaban 2 hour or more prior to hemodialysis, instruct the patient to take the apixaban as early as is feasible, and instruct patient to note the time he or she takes the dose of apixaban. The timing of the apixaban dose needs to be noted in the CRF.
- For patients randomized to warfarin, instruct patient to take medication as prescribed.

8.2 Day 1 Visit (Enrollment)

Day 1 visit is the first hemodialysis visit after the patient commences study drug treatment. The Day 1 **visit should occur within 3 days or randomization or as soon as the INR value is < 2.0 in the case of patients on warfarin at the time of enrollment, who were randomized to apixaban (Appendix 3).**

The investigator or designee will:

- Obtain vital signs
- For patients enrolled using protocol version 13 or earlier, obtain biomarker sample (if biomarker sample is not able to be drawn at the Day 1 visit, it can be drawn at a subsequent visit). For patients enrolled using protocol version 14, no biomarker sample will be collected.
- Review concomitant medications and record any concomitant medications potentially related to dialysis (hematopoietic agents), or bleeding (SSRIs, aspirin; P2Y12 antagonists such as clopidogrel, prasugrel, and ticagrelor; NSAIDs)
- Assess for any AEs of special interest (thrombosis of fistula, graft, or access catheter; thrombosis of extracorporeal dialysis circuit; access site bleeding) that have occurred since time of consent
- Assess for any SAEs, major bleeding events, clinically relevant non-major bleeding events, strokes, systemic emboli, or deaths since time of randomization
- Record start and stop time of hemodialysis session
- For patients receiving apixaban and enrolled using version 13 or earlier, PK samples were collected. For patients enrolled using version 14, no PK samples will be collected.

- Record time of the most recent apixaban dose prior to the PK sample
- If the patient was taking apixaban at the time of enrollment, record the approximate date that the patient originally started their apixaban prior to enrollment in the study
- Obtain 2 PK blood samples. PK samples are to be obtained at the start of the hemodialysis session, and at the end of the hemodialysis session. It is preferred if apixaban is taken at least 2 hours prior to the start of the hemodialysis session; however, if this is not feasible, the PK sample should still be taken. For all PK blood samples, it is necessary to document the time at which the PK blood sample and the time at which the last dose of apixaban prior to the PK blood sample were taken.

8.3 Day 3 Visit (Day 3, 4, 5, or 6 depending on hemodialysis session schedule) [Appendix 3]

Investigator or designee will:

- Obtain vital signs
- Review concomitant medications and record any concomitant medications potentially related to dialysis (hematopoietic agents), or bleeding (SSRIs, aspirin; P2Y12 antagonists such as clopidogrel, prasugrel, and ticagrelor; NSAIDs)
- Assess for any AEs of special interest (thrombosis of fistula, graft, or access catheter; thrombosis of extracorporeal dialysis circuit; access site bleeding) that have occurred since last visit
- Assess for any SAEs, major bleeding events, clinically relevant non-major bleeding events, strokes, systemic emboli, or deaths since time of randomization
- Record start and stop time of hemodialysis session
- For patients randomized to apixaban who are participating in the PK/PD subset, which only includes patients enrolled using protocol version 13 or earlier
  - Record time of apixaban dose. Apixaban should be taken at least 2 hours prior to the start of the hemodialysis session.
  - Obtain 2 blood samples for PK/PD analysis. Samples are to be obtained at the start of the dialysis session, and at the end of the dialysis session.

8.4 Month 1 Visit (± 4 days)

Investigator or designee will:

- Review concomitant medications and record any concomitant medications potentially related to dialysis (hematopoietic agents), or bleeding (SSRIs, aspirin; P2Y12 antagonists such as clopidogrel, prasugrel, and ticagrelor; NSAIDs)

- Assess for any SAEs or AEs of special interest (thrombosis of fistula, graft, or access catheter; thrombosis of extracorporeal dialysis circuit; access site bleeding) that have occurred since last visit
- Assess for any major bleeding events, clinically relevant non-major bleeding events, strokes, systemic emboli, or deaths since last visit
- Obtain vital signs
- Obtain laboratory measures
    - Record most recent CBC data for for all patients
    - INR for patients receiving warfarin
- Record start and stop time of hemodialysis session
- For patients randomized to apixaban who are participating in the PK subset, which only includes patients enrolled using protocol version 13 or earlier
    - Record time of apixaban dose
    - Obtain 2 blood samples for PK/PD analysis. Samples are to be obtained at the start of the dialysis session, and at the end of the dialysis session.

8.5 Month 2 (± 4 days)

Investigator or designee will:

- Review concomitant medications and record any concomitant medications potentially related to dialysis (hematopoietic agents), or bleeding (SSRIs, aspirin; P2Y12 antagonists such as clopidogrel, prasugrel, and ticagrelor; NSAIDs)
- Assess for any SAEs or AEs of special interest (thrombosis of fistula, graft, or access catheter; thrombosis of extracorporeal dialysis circuit; access site bleeding) that have occurred since last visit
- Assess for any major bleeding events, clinically relevant non-major bleeding events, strokes, systemic emboli, or deaths since last visit
- Obtain vital signs
- Obtain laboratory measures
    - Record most recent CBC data for all patients
    - INR for patients receiving warfarin
- Record start and stop time of hemodialysis session

8.6 Month 3, Month 6, Month 9, and Month 12 (± 4 days)

Investigator or designee will:

- Review concomitant medications and record any concomitant medications potentially related to dialysis (hematopoietic agents), or bleeding (SSRIs, aspirin; P2Y12 antagonists such as clopidogrel, prasugrel, and ticagrelor; NSAIDs)

- Assess for any SAEs or AEs of special interest (thrombosis of fistula, graft, or access catheter; thrombosis of extracorporeal dialysis circuit; access site bleeding) that have occurred since last visit
- Assess for any major bleeding events, clinically relevant non-major bleeding events, strokes, systemic emboli, or deaths since last visit
- Obtain vital signs
- Obtain laboratory measures
    - Record most recent CBC data for all patients
    - INR for patients receiving warfarin
- Assess medication compliance for apixaban: conduct pill count
- Record responses to medication adherence questions
- Dispense study medication (apixaban treatment group) or prescription (warfarin treatment group)
- Record start and stop time of hemodialysis session

8.7 Month 15 or Final Visit (+ 4 days)

Investigator or designee will:

- Review concomitant medications and record any concomitant medications potentially related to dialysis (hematopoietic agents), or bleeding (SSRIs, aspirin; P2Y12 antagonists such as clopidogrel, prasugrel, and ticagrelor; NSAIDs)
- Assess for any SAEs or AEs of special interest (thrombosis of fistula, graft, or access catheter; thrombosis of extracorporeal dialysis circuit; access site bleeding) that have occurred since last visit
- Assess for any major bleeding events, clinically relevant non-major bleeding events, strokes, systemic emboli, or deaths since last visit
- Obtain vital signs
- Measure dry body weight or hemodialysis target body weight
- Obtain laboratory measures
    - Record most recent CBC data for all patients
    - INR for patients receiving warfarin
- Assess medication compliance for apixaban: conduct pill count
- Record responses to medication adherence questions
- Record start and stop time of hemodialysis session

8.8 Discontinuation of Patient from Study

Patients can decide to withdraw from the study for any reason. If the patient withdraws consent to be contacted for follow-up, vital status will be obtained through the patients records,

physician, or public records. When allowed and with consent, social security number will be obtained as to allow obtaining vital status through National Death Index and/or Medicare.

9 ADVERSE EVENTS

An Adverse Event [AE] is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation patient administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

9.1 Safety Management

The sponsor has engaged DCRI Safety Surveillance to oversee real-time serious adverse event (SAE) collection, evaluation, and expedited regulatory reporting for this study. A DCRI safety medical monitor will be responsible for evaluating site reported SAEs to confirm protocol specific serious reporting criteria, causality assessment, and expectedness compared to the product label. Details of this process can be found in the study-specific Safety Management Plan.

9.2 Suspected Adverse Reaction

A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the drug caused the event. “Reasonable possibility” suggests there is a causal relationship between the drug and the adverse event. “Suspected adverse reaction” implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Adverse events, except as described below, will not be collected since both study drugs are marketed and have known and extensive safety profiles.

9.3 Serious Criteria

For this protocol, a Serious Adverse Event (SAE) is any untoward medical occurrence at any dose that:

- results in death
- is life-threatening (defined as an event in which the patient 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
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.
- results in potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be submitted to the sponsor within the same time period as an SAE.

9.3.1 Events of Special Interest

The following events will not be included in the primary outcome, but they are clinical events of special interest that may relate to safety and that will be tracked and reported in the trial results. These adverse events are to be reported to DCRI, regardless of whether these reports are classified as serious or unexpected:

- Thrombosis of fistula, graft, or access catheter
- Thrombosis of extracorporeal dialysis circuit
- Access site bleeding that does not meet the criteria for major or clinically relevant non-major bleeding, as defined in Section 0
- Other clinically overt bleeding that does not meet the criteria for major or clinically relevant non-major bleeding, as defined in Section 0
- Red blood cell transfusion(s)

9.3.2 Protocol Specific Exceptions to SAE Reporting

The following SAEs will be collected but do not require reporting through the SAE reporting mechanism. These events will be captured on event-specific forms, not on the SAE form

- Safety and efficacy outcomes that are being collected in a systematic way on the eCRF, such as major bleeding, clinically relevant non-major bleeding, stroke or systemic embolism, and mortality will be collected and recorded within the database
- Other clinical outcomes expected to occur in patients on hemodialysis as part of the disease process:
    - Myocardial infarction
    - Atrial fibrillation with rapid ventricular response
    - Heart failure or fluid overload
    - Pulmonary edema
    - Transient ischemic attack

- Acute severe hypertension
- Infections (including but not limited to cellulitis, osteomyelitis, and pneumonia)

- NOTE: Outcomes that are expected to occur in patients on hemodialysis as part of the disease process that are not clinically relevant to the trial need not be collected or reported: hyperkalemia, hypoglycemia in patients with diabetes, bradycardia, peripheral arterial disease or gangrene, chronic obstructive pulmonary disease, constipation, hypotension, or long bone fracture such as femur fracture.

NOTE: The following hospitalizations are not considered SAEs:

- Visits to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- Elective surgery planned before or after signing consent
- Admissions as per protocol for a planned medical/surgical procedure or elective surgeries.
- Routine health assessments requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- Medical/surgical admissions other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- Admissions encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

9.4 Assessment of Adverse Event Severity

The determination of adverse event severity rests on medical judgment of a medically-qualified investigator. The severity of AEs will be graded using the following definitions:

Mild: awareness of sign, symptom, or event, but easily tolerated;

Moderate: discomfort enough to cause interference with usual activity and may warrant intervention;

Severe: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

9.5 Assessment of Causal Relationship

The causal relationship to study drug is to be determined by a physician at the site and should be used to assess all reportable adverse events (AEs).

The causal relationship should be one of the following:

- **Related:** There is 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 adverse event.

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

The investigator reports causality, but the sponsor retains the final decision on causality when filing to the FDA.

9.6 Expectedness

The expectedness of an adverse event shall be determined according to the specified reference document containing safety information (e.g., most current investigator's brochure or product label). Any AE that is not identified in nature, severity, or specificity in the current study drug reference document(s) (e.g. investigator's brochure), is considered unexpected/unlisted. Events that are mentioned in the investigator's brochure or product label as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation or on the list of expected events (Appendix 4) in the course of illness of patients with atrial fibrillation on hemodialysis are considered unexpected/unlisted.

9.7 Adverse Event Collecting and Reporting

Non-serious adverse events that lead to permanent discontinuation of study drug will be collected on the eCRF.

Following the patient's signing the written consent in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur after signing the written consent through 30 days after permanent study drug discontinuation. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All Serious Adverse Events (SAEs) that occur following the subject's written consent in the study through 30 days after permanent study drug discontinuation must be reported to DCRI.

SAEs, whether related or unrelated to the study drug, and pregnancies must be reported by the site to DCRI within 24 hours through the electronic data capture system (EDC). DCRI will report the SAE to BMS within 2 business days via a protocol-specific SAE page generated through

the EDC. Pregnancies must be reported by the site to DCRI on a Pregnancy Surveillance Form. **NOTE: DCRI will forward any pregnancy information to BMS within 2 business days. SAE email address and fax number as listed are only for DCRI to report to BMS, and not for direct site reporting.**

SAE Email Address: Worldwide.Safety@BMS.com.
SAE Fax Number: 609-818-3804.

If only limited information is initially available, follow-up reports are required. Note: Follow-up SAE reports should include the same investigator term(s) initially reported.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to DCRI using the same procedure used for transmitting the initial SAE report.

All SAEs will be followed until resolution, stabilization or the event is otherwise explained.

If the investigator believes that an SAE (that needs to be reported as such) is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Form.

All SAEs must be reported by the investigator or qualified designee within 24 hours of becoming aware of the event. The investigator/qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF, which will automatically result in distribution of the information to the appropriate sponsor contact. If the eCRF system is temporarily unavailable, the event, including the investigator-determined causality to study drug, should be reported via a paper back-up SAE form to DCRI. Upon return of the availability of EDC system, the SAE information must be entered into the eCRF within 24 hours.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must submitted within the same time period (1 business day) as an SAE.

9.7.1 SAE Reconciliation performed by DCRI

DCRI 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 DCRI, 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 DCRI determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

9.7.2 Follow-up

When additional relevant information becomes available, the investigator will record follow-up information according to the same process used for reporting the initial event as described above. The investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained.

The Sponsor or designee (e.g. DCRI Safety Surveillance) will follow all SAEs and pregnancies until resolution, stabilization, until otherwise explained.

9.8 Health Authority Reporting (US FDA IND)

Investigators must adhere to local Health Authority Reporting Requirements. For studies conducted under an investigator sponsored US FDA IND, the FDA will be provided information on the following through the DCRI:

- Any event that is both serious and unexpected will be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information.

9.8.1 Expedited events

The Sponsor or designee will notify the FDA and all participating investigators in a written IND safety report of an SAR that, based on the opinion of the investigator or sponsor, is serious, is related to study drug, and is unexpected (per the sponsor) as soon as possible, but not later than 15 calendar days after the sponsor has determined the serious, unexpected SAR (SUSAR) qualifies for expedited reporting. The sponsor will identify all safety reports previously filed with the IND concerning a similar SAR, and will analyze the significance of the SAR in light of the previous, similar reports. Follow-up reports will be sent to investigators to inform and update them about an important suspected adverse reaction if it significantly affects the care of the patients or conduct of the study.

The site investigator will be responsible for reporting adverse events and unanticipated problems involving risks to patients to their local IRBs/IECs in accordance with local regulations.

9.8.2 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

A non-serious adverse event is an AE that is not classified as serious. Non-serious adverse events will only be collected if they result in study drug discontinuation or if they are predefined outcomes (or other events of special interest) that will be collected as outcome clinical events in the trial eCRFs. The collection of other non-serious adverse event (NSAE) will not be done during this pragmatic clinical trial. Non-serious AEs that are collected during the study will be listed in the Clinical Study Report (CSR).

9.9 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured and reported as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the patient to have study drug discontinued

It is expected that wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (e.g., use the term anemia rather than low hemoglobin value).

Laboratory test abnormalities are provided to the sponsor via annual safety reports (if applicable), and interim or final study reports.

9.10 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study patient 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 (e.g. dose tapering if necessary for patient safety).

The investigator must immediately notify the sponsor of this event within 24 hours and in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Any associated AEs or SAEs that occur to the mother or fetus/child will be recorded in the SAE eCRFs.

Any pregnancy that occurs in a female partner of a male study patient should be reported to DCRI. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form. DCRI will forward reports to BMS.

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

It is expected that whenever possible, the clinical, rather than the laboratory, term would be used by the reporting investigator (e.g., anemia vs. low hemoglobin value).

9.11 Overdose

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

10 DATA MONITORING COMMITTEE

The data monitoring committee (DMC) will monitor the safety aspects of this study. The DMC will consist of clinicians and one statistician. The DMC is expected to meet at approximately every 6-months. The DMC charter will provide details on monitoring roles and responsibilities.

11 CLINICAL EVENTS CLASSIFICATION

The DCRI Clinical Events Classification (CEC) group will be responsible for blindly adjudicating the primary endpoint of major bleeding or clinically relevant non-major bleeding. The CEC will also adjudicate secondary outcomes as defined in Section 0. Source documents will be collected as part of this blind, adjudication process. The methodology used by the CEC is detailed in the CEC charter.

12 STATISTICAL CONSIDERATIONS

12.1 Sample Size Determination

No confirmatory statistical hypothesis testing is pre-specified, and the explotorary analyses will be detailed in a separate statistical analysis plan (SAP). The SAP will be based on deriving the point estimates and 95% CIs for the pairwise comparisons of the primary endpoint, as well as other clinical outcomes of interest. These comparisons will be presented as a two-sided 95% CI on the observed relative risk (hazard ratio). For the primary endpoint, Kaplan-Meier cumulative risk curves will be constructed and log-rank test will be used.

The trial will randomize approximately 230 patients in a ratio of 1:1 to warfarin or apixaban treatment groups. Radomization will be stratified by investigative site and prior warfarin status (experienced versus naïve). The study will be conducted at about 65 sites in the United States. The primary endpoint is major bleeding or clinically relevant non-major bleeding.

Due to a lower recruitment rate than anticipated in the early stage in the trial, the sample size was reduced from 760 (see protocol version 13, Section 12.1) to 230 patients. Due to lack of statistical power with a total of 230 patients, the current analytic plan has been changed from a formal non-inferiority testing followed by superiority testing to an exploratory analytic plan with no confirmatory statistical hypothesis testing. If the upper 95% CI on the relative risk of the primary outcome excludes 1.40, this will be considered evidence of non-inferiority of apixaban. However, if the 95% CI excludes unity, this would be considered evidence of superiority.

The 30% event rate in warfarin patients is based on the fact that the major bleeding rate for patients in ARISTOTLE with an estimated creatinine clearance of 30mL/min, who were randomized to warfarin, was approximately 10% at 1-year.[17] The major or clinically relevant non-major bleeding rate would be estimated to be 20% at 1 year for patients with an estimated

creatinine clearance of 30mL/min based on the fact that clinically relevant non-major bleeding in ARISTOTLE occurred at the same rate as major bleeding.[9] Similarly the rate of major bleeding was 13% in ARISTOTLE patients 75 years or older with an estimated creatinine clearance less than or equal to 30mL/min.[22] In the ROCKET trial, the rate of major or clinically relevant non-major bleeding in patients with an estimated creatinine clearance of 30-49mL/min was 18% per year.[23] The assumption is that there is approximately 1.5 times more bleeding in hemodialysis patients relative to patients with an estimated creatinine clearance of 30mL/min. This is further supported by a 34% rate of non-access site major bleeding among warfarin patients, which was noted in a retrospective analysis of hemodialysis patients with AF.[11]

12.2 Populations for Analyses

The primary outcome will be calculated based on an intention to treat (ITT) methodology. The ITT approach uses all randomized patients analyzed by treatment assigned. A sensitivity analysis is planned using the "modified intention to treat (mITT)". The mITT population uses all randomized patients who received at least 1 dose of study therapy analyzed by randomized treatment.

The DMC may choose to look at the 'safety' population defined as the mITT population analyzed by the initial drug received. Details will be provided in the DMC SAP.

12.3 Outcome Definitions

The primary outcome is major bleeding or clinically relevant non-major bleeding. Major bleeding described below is adapted from the International Society on Thrombosis and Hemostasis (ISTH) definition in order to be relevant for this specific AF ESRD patient population treated with hemodialysis.

A major bleeding event is defined as:

- Acute clinically overt bleeding (including access site related bleeding) accompanied by one or more of the following:
    - A decrease in hemoglobin of 2g/dL or more with overt bleeding (over a period deemed by the events review process to be consistent with bleeding)
    - A transfusion of 2 or more units of packed red blood cells in the setting of an overt bleeding event (over a period deemed by the events review process to be consistent with bleeding)
    - Bleeding at a critical site
        - Intracranial
        - Intra-spinal
        - Intraocular
        - Pericardial

- Intra-articular
- Intramuscular with compartment syndrome
- Retroperitoneal
- Fatal bleeding

Clinically relevant non-major bleeding event:

- Acute or sub-acute clinically overt bleeding (including access site related bleeding) that does not meet criteria for major bleeding and results in:
  - Hospital admission for bleeding
  - Physician guided medical or surgical treatment for bleeding
  - A change in antithrombotic therapy

Safety events of special interest: these events will not be included in the primary endpoint, but they are safety events of special interest that will be tracked. These events are defined in section 9.3.1.

This is primarily a safety outcome trial. The efficacy outcomes are secondary outcomes, as listed below.

- Stroke: Diagnosis of stroke will require the abrupt onset of focal neurological symptoms lasting at least 24 hours. It is strongly recommended (but not required) that a neurologist evaluation supports the diagnosis of stroke. An imaging procedure such as a head CT scan or MRI should support the diagnosis of stroke, as made by the neurologist. All strokes will be classified as stroke of unknown cause, ischemic, or hemorrhagic.
- Systemic embolism: Clinical history consistent with an acute loss of blood flow to a peripheral artery, which is supported by evidence of embolism from surgical specimens, autopsy, angiography, ultrasound, or other objective testing.
- All-cause mortality: Deaths will be classified as either cardiovascular or non-cardiovascular. All deaths will be assumed to be cardiovascular unless a non-cardiovascular cause can be clearly provided

12.4 Analyses

12.4.1 Demographics and Baseline Characteristics

Frequency distribution and summary statistics for demographic and baseline variables will be presented by treatment group and for all patients combined. Key demographic and baseline variables to be summarized include: geographic region, age, sex, race/ethnicity, vintage (time since initiation of dialysis), height, dry body weight or hemodialysis target body weight, Quételet's (body mass) index (BMI), vital signs, prior warfarin status (experienced versus naïve), risk factors

for stroke, risk factors for bleeding, comorbid conditions, baseline medications, and atrial fibrillation type.

12.4.2 Analysis for Primary Safety Endpoint

The primary objective is to assess the safety of apixaban as compared to warfarin on the primary safety outcome defined as time to first occurrence of major bleeding or clinically relevant non-major bleeding during the study period among all randomized patients. The Cox proportional hazards model, stratified by prior warfarin status (experienced versus naïve) on the intent to treat (ITT) population will be used as the primary analysis to evaluate the endpoint. This analysis will be repeated after adjusting for clinically important baseline characteristics to be specified in the statistical analysis plan (SAP).

The validity of the proportional hazard assumption underlying the Cox survival analysis will be tested using appropriate statistical methods. If required, additional appropriate survival analysis techniques will be employed as sensitivity analyses. Evaluation of the primary safety outcomes will include events which occurred from the randomization date to the month 15 visit or the date of final assessment where all elements of the outcome of interest were evaluated if that is prior to the month 15 visit, regardless of the time interval between patient discontinuation of study drug and final contact. If patients do not have any events throughout the study, they will be censored on the date of final assessment where all elements of the outcome of interest were evaluated.

Subgroup analyses will be performed to further evaluate apixaban effect. Relevant subgroups, including age, sex, race, aspirin use, concomitant medications, and medical history, will be examined and will be pre-specified in greater detail in the Statistical Analysis Plan (SAP). Hazard ratios and 95% confidence intervals will be reported for each subgroup, as well as p-values for the tests of interaction between treatment and each subgroup.

In addition to the ITT populations, the analyses for the primary safety endpoint will be performed on the mITT. Additional details will be provided in the SAP, which will be developed prior to the first DMC analysis and finalized prior to study completion.

12.4.3 Efficacy Analyses

Event rates for the following secondary outcomes will be summarized by treatment group:

- Ischemic stroke
- Hemorrhagic stroke
- Stroke of unknown cause
- Systemic embolism
- All-cause death
- Composite of stroke or systemic embolism

- Composite of stroke, systemic embolism, major bleeding, and all-cause mortality

Cox proportional hazards models will be used to estimate the hazard ratios and two-sided 95% confidence intervals for each of these secondary outcomes.

12.4.4 Persistence and Adherence Analyses

A single-item self-reported medication adherence question that has been associated with hospitalization and death in cardiovascular patients will be asked of all patients in order to provide a direct comparison between the adherence of the apixaban and warfarin patients: "Out of the past 7 days, did you miss a dose of your blood thinner?"[20]

A second self-reported adherence question will also be asked: "Over the last 30 days, how often have you taken your blood thinner: less than 20% (5 days or fewer), 20-80% (6 days to 23 days), or greater than 80% (24 days or more) of the time?"[21] This data will be collected at the quarterly visits.

The TTR will be determined by the modified Rosendaal method of linear interpolation between each pair of measured INR values.[25]

More details on the statistical methods and analyses will be provided in the statistical analysis plan (SAP).

12.4.5 Pharmacokinetic and Pharmacodynamic Analyses

Samples will be obtained from a subset of patients randomized to apixaban, under versions 13 or earlier of the protocol, to characterize apixaban PK/PD levels in hemodialysis patients with atrial fibrillation. No patients enrolled under version 14 of the protocol will have PK/PD samples collected. Details for analyses will be specified in a separate PK/PD SAP.

- Pharmacokinetic Measures:
    - Samples collected as described in Study Assessments and Procedures will be analyzed to determine apixaban plasma concentration. Listing of the apixaban plasma concentrations will be provided.
    - Data from the current study may be pooled with historical data to provide individual PK parameters (e.g., CL/F, Vc/F, KA) in order to approximate Cmax, Cmin, and AUC (TAU) for each patient from a PPK model. Modeling results will be reported separately.
- Pharmacodynamic Measures:
    - Samples collected as described in Study Assessments and Procedures will be analyzed by a one-step chromogenic anti-FXa assay. Listing of the anti-FXa activities will be provided.

12.4.6 Biomarker Analyses

At the Day 1 visit, a blood sample will be collected from a subset of patients, enrolled using versions 13 or earlier of the protocol, and stored for later measurement of selected biomarkers. If the biomarker sample is not able to be drawn at the Day 1 visit, it can be drawn at a subsequent visit. Blood samples will be analyzed for biomarkers such as, but not limited to, NTproBNP, hsTn, GDF-15. The biomarker evaluation will be used to characterize the risk of clinical outcomes, such as bleeding, in patients with NVAF and ESRD on hemodialysis. No patients enrolled using version 14 of the protocol will have a blood sample collected.

13 STUDY MANAGEMENT

13.1 Compliance with the Protocol

The study shall be conducted as described in this approved protocol. The sponsor is the sole authority of the content of this protocol and any revisions to the protocol will be at the sponsor's discretion. The site investigator will not implement any deviation or change to the protocol without prior review and documented approval of the amendment from the appropriate IRB, except when necessary to eliminate an immediate hazard(s) to study patients.

13.2 Records Retention

13.2.1 Study and Source Document Records Retention

The investigator must retain all study records and source documents for a minimum of 2 years or longer, if notified by the sponsor, following the completion of the study, unless local regulations and institutional policies require a longer storage period.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to the sponsor.

13.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product is maintained at each study site where study drug and non-investigational product(s) is/are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each patient, including unique patient identifiers
- amount transferred to another area/site for dispensing or storage

- non-study disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

13.3 Destruction of Investigational Product

Study drugs are to be destroyed on site. It is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

14 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor to be related to the investigational product
Expedited Safety Report	Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the Investigator Brochure), or that could be associated with the study procedures.
SUSAR	Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC).
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved investigational product)

15 LIST OF ABBREVIATIONS

AE	Adverse Event
AF	Atrial fibrillation
BMS	Bristol-Myers Squibb
CEC	Clinical Events Classification
eCRF	(electronic) Case Report Form
EDC	Electronic Data Capture
ESRD	End stage renal disease
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISR	Investigator-Sponsored Research
ITT	Intent to treat
NCI	National Cancer Institute
NSAE	Non-Serious Adverse Event
NVAF	Non-valvular atrial fibrillation
RDW	Red Cell Distribution Width

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient ischemic attack
TTR	Time in Therapeutic Range
WOCBP	Women of Child-Bearing Potential

16 REFERENCES

1. Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, Kerr PG, Young EW, Robinson BM. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int 2010;77(12):1098-106.
2. Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 2012;367(7):625-35.
3. Nigwekar SU, Bhan I, Turchin A, Skentzos SC, Hajhosseiny R, Steele D, Nazarian RM, Wenger J, Parikh S, Karumanchi A, Thadhani R. Statin use and calcific uremic arteriolopathy: a matched case-control study. Am J Nephrol 2013;37(4):325-32.
4. Yang F, Chou D, Schweitzer P, Hanon S. Warfarin in haemodialysis patients with atrial fibrillation: what benefit? Europace 2010;12(12):1666-72.
5. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol 2009;20(10):2223-33.
6. Shah M, Avgil Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Humphries KH, Tu JV, Behlouli H, Guo H, Pilote L. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation 2014;129(11):1196-203.
7. Granger CB, Chertow GM. A pint of sweat will save a gallon of blood: a call for randomized trials of anticoagulation in end-stage renal disease. Circulation 2014;129(11):1190-2.
8. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364(9):806-17.
9. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981-92.
10. Product Monograph PrELIQUIS (apixaban). In: Inc PC, (ed); 2011.
11. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and Rivaroxaban Use in Atrial Fibrillation Patients on Hemodialysis. Circulation 2015.
12. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. Clin J Am Soc Nephrol 2011;6(11):2599-604.

13. Herzog CA, Asinger RW, Berger AK, Charytan DM, Diez J, Hart RG, Eckardt KU, Kasiske BL, McCullough PA, Passman RS, DeLoach SS, Pun PH, Ritz E. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80(6):572-86.
14. Reinecke H, Brand E, Mesters R, Schabitz WR, Fisher M, Pavenstadt H, Breithardt G. Dilemmas in the management of atrial fibrillation in chronic kidney disease. J Am Soc Nephrol 2009;20(4):705-11.
15. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857-67.
16. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. Clin J Am Soc Nephrol 2011;6(11):2662-8.
17. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, Keltai M, Lanas F, Lopes RD, Lopez-Sendon J, Granger CB, Wallentin L. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J 2012.
18. US Renal Data System. USRDS 2014 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014. http://www.usrds.org/adr.aspx. United States Renal Data System Web site. Accessed June 2, 2015.
19. Elliott MJ, Zimmerman D, Holden RM. Warfarin anticoagulation in hemodialysis patients: a systematic review of bleeding rates. Am J Kidney Dis 2007;50(3):433-40.
20. Wu JR, DeWalt DA, Baker DW, Schillinger D, Ruo B, Bibbins-Domingo K, Macabasco-O'Connell A, Holmes GM, Broucksou KA, Erman B, Hawk V, Cene CW, Jones CD, Pignone M. A single-item self-report medication adherence question predicts hospitalisation and death in patients with heart failure. J Clin Nurs 2014;23(17-18):2554-64.
21. Gonzalez JS, Schneider HE, Wexler DJ, Psaros C, Delahanty LM, Cagliero E, Safren SA. Validity of medication adherence self-reports in adults with type 2 diabetes. Diabetes Care 2013;36(4):831-7.
22. Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, Granger CB, Hanna M, Held C, Husted S, Hylek EM, Jansky P, Lopes RD, Ruzyllo W, Thomas L, Wallentin L. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. Eur Heart J 2014;35(28):1864-72.
23. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, Paolini JF, Hankey GJ, Mahaffey KW, Patel MR, Singer DE, Califf RM. Prevention of stroke and systemic

embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J 2011;32(19):2387-94.

24. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 1990;9(12):1447-54.
25. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69(3):236-9.
26. Savaysa ® (edoxaban) [package insert] Daiichi Sankyo, Inc,, Parsippany, NJ. September 2016.

17 APPENDICES

Appendix 1: CHA2DS2-VASc Score

C: Congestive Heart Failure (1 point)

H: Hypertension (1 point)

A2: Age ≥ 75 years (2 points)

D: Diabetes mellitus (1 point)

S2: Stroke or TIA (2 points)

V: Vascular disease: previous MI, peripheral arterial disease or aortic plaque (1 point)

A: Age 65-74 years (1 point)

Sc: Female sex (1 point)

Appendix 2: Schedule of Procedures

Procedure	(Screening & Randomization)	Day 1[1]	Day 3[2] (Day 3, 4, 5, or 6)	Month 1 (± 4 days)	Month 2 (± 4 days)	Month 3, 6, 9, 12 (± 4 days)	Month 15 (+ 4 days) or Final Visit
Informed Consent	X						
Eligibility review	X						
Medical History Review	X						
Vital signs[3]	X	X	X	X	X	X	X
Height	X						
Dry body weight or hemodialysis target body weight	X						X
ECG[4]	X						
SAE, AEs of special interest, and bleeding event assessment	X[5]	X	X	X	X	X	X
Con med assessment	X	X	X	X	X	X	X
Pregnancy prevention counseling	X						
Randomize in EDC system	X						
Dispense or prescribe and instruct on use of drug	X					X	

Procedure	(Screening & Randomization)	Day 1[1]	Day 3[2] (Day 3, 4, 5, or 6)	Month 1 (± 4 days)	Month 2 (± 4 days)	Month 3, 6, 9, 12 (± 4 days)	Month 15 (+ 4 days) or Final Visit
Medication Compliance Assessment						X	X
Record start and stop time of hemodialysis session		X	X	X	X	X	X
Record time of apixaban dose		X	X	X			
CBC[6]	X			X	X	X	X
BMP	X						
INR[7]	X			X	X	X	X
Urine or serum β-hCG[8]	X						
Pharmacokinetic Sample[9]		X	X	X			
Biomarker Sample[10]		X					

[1] Visit should occur within 3 days of randomization or as soon as the INR value is < 2.0 in the case of patients on warfarin at the time of enrollment, who were randomized to apixaban

[2] Visit may occur on Day 3, 4, 5, or 6 depending on hemodialysis session

[3] Resting blood pressure, pulse, respiratory rate, and temperature

[4] After resting for ≥ 5 minutes, at enrollment or within 30 days of enrollment. May include a single lead rhythm strip such as AliveCor.

[5] SAEs that occur anytime after consent, including between consent and randomization, must be reported

[6] Includes hematocrit, hemoglobin (Hb), platelet count, red blood cell count (RBC), red cell distribution width (RDW). Results from most recent standard of care draw may be used, if results are not > 30 days old.

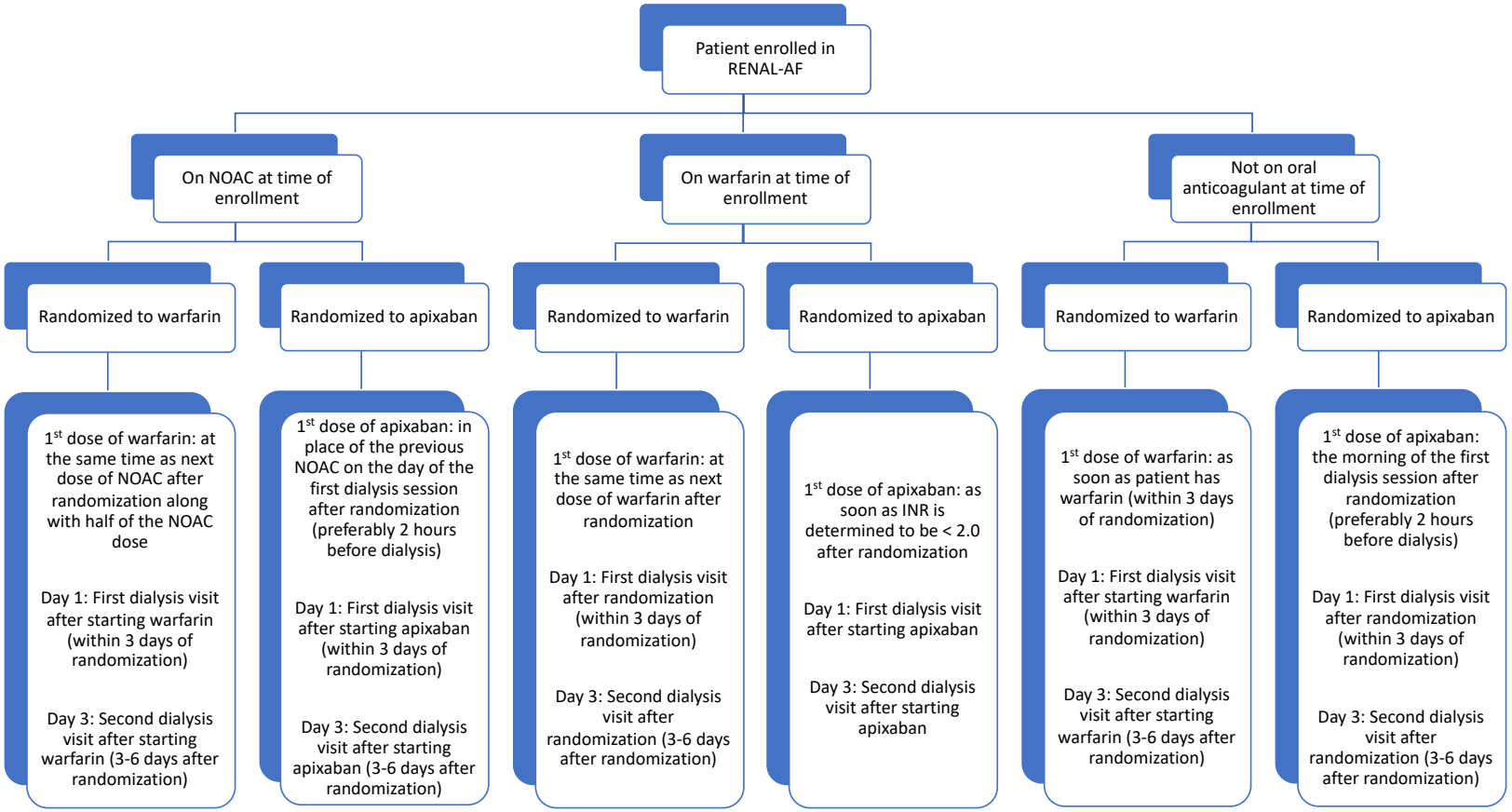
[7] Includes International Normalized Ration (INR). INR should be performed at least monthly for patients randomized to warfarin, and at screening and randomization for all patients.

[8] If positive, patient is not eligible to participate. If patient is anuric, a serum pregnancy test can be performed.

[9] At Day 1 visit, PK samples are to be collected for all patients randomized to apixaban: at the start of the hemodialysis session and at the end of the hemodialysis session. A sub-set of 50 patients randomized to the apixaban arm will have additional PK samples, and a PD sample, drawn at the Day 3 (between day 3 and day 6) and Month 1 visits. Samples are to be collected at the start of the hemodialysis session, and at the end of the hemodialysis session. This is only for patients enrolled using versions 13 or earlier of the protocol. No samples will be collected for patients enrolled using version 14 of the protocol.

[10] If the biomarker sample is not able to be drawn at the Day 1 visit, it can be drawn at a subsequent visit. This is only for patients enrolled using versions 13 or earlier of the protocol. No samples will be collected for patients enrolled using version 14 of the protocol.

Appendix 3: Timing of First Dose, Day 1, and Day 3



Appendix 4: Expected Events in Patients on Hemodialysis

- Myocardial infarction
- Atrial fibrillation with rapid ventricular response
- Heart failure or fluid overload
- Pulmonary edema
- Transient ischemic attack
- Acute severe hypertension
- Infections (including but not limited to cellulitis, osteomyelitis, and pneumonia)
- Hyperkalemia
- Hypoglycemia in patients with diabetes
- Bradycardia
- Peripheral arterial disease or gangrene
- Chronic obstructive pulmonary disease
- Constipation
- Hypotension
- Long bone fracture such as femur fracture