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Trial Design

An open-Label, 2 × 2 factorial, randomized controlled trial to evaluate the safety of apixaban vs. vitamin K antagonist and aspirin vs. placebo in patients with atrial fibrillation and acute coronary syndrome and/or percutaneous coronary intervention: Rationale and design of the AUGUSTUS trial

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ABSTRACT

Background: The optimal antithrombotic strategy for patients with atrial fibrillation (AF) who develop acute coronary syndrome (ACS) and/or the need for percutaneous coronary intervention (PCI) is uncertain. The risk of bleeding is a major concern when oral anticoagulation is required to prevent stroke, and concomitant therapy with antiplatelet agents is required to minimize recurrent ischemic events.
Design: AUGUSTUS is an international, multicenter randomized trial with a 2 × 2 factorial design to compare apixaban with vitamin K antagonists and aspirin with placebo in patients with AF who develop ACS and/or undergo PCI and are receiving a P2Y12 inhibitor. Patients will be evaluated for eligibility during their ACS and/or PCI hospitalization. The primary outcome is the composite of major and clinically relevant nonmajor bleeding defined by the International Society on Thrombosis and Haemostasis. A key secondary outcome is the composite of all-cause death and all-cause hospitalization. Other secondary objectives are to evaluate ischemic outcomes including the composite of death, myocardial infarction, stroke, stent thrombosis, urgent revascularization, and all-cause hospitalization and each individual component. The aim is to enroll approximately 4,600 patients from around 500 sites in 33 countries.
Summary: AUGUSTUS will provide insight into the optimal oral antithrombotic therapy strategy for patients with AF and concomitant coronary artery disease. The unique 2 × 2 factorial design will delineate the bleeding effects of various anticoagulant and antiplatelet therapies and generate evidence to guide the selection of the optimal antithrombotic regimen for this challenging group of patients. It is the largest and only prospective randomized trial to investigate in a blinded fashion the risk and benefits of aspirin on top of a non–vitamin K antagonist oral anticoagulant and P2Y12 receptor inhibition.

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with increasing prevalence among the elderly.[1] Approximately 20%-30% of patients with AF also have concomitant coronary artery disease (CAD),[2,3] and 5%-10% of patients who undergo percutaneous coronary intervention (PCI) have AF.[4-7] A clinical conundrum arises when patients with AF on oral anticoagulation develop an acute coronary syndrome (ACS) and/or require PCI. Vitamin K antagonists (VKAs) have not been shown to prevent stent thrombosis and are not indicated for secondary prevention following an ACS, whereas dual antiplatelet therapy (DAPT) does not provide a large treatment effect in preventing AF-related strokes.[8,9] The addition of dual antiplatelet agents to VKA

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("triple therapy") significantly increases the risk of bleeding.[10,11] Thus, there is a significant unmet need for an oral antithrombotic strategy with an acceptable benefit/risk profile for the treatment of patients with AF and concomitant acute CAD.

A triple-therapy strategy in patients on DAPT requiring oral anticoagulation has been called into question with the publication of the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StentTing (WOEST) trial, the first trial in which patients undergoing PCI on oral anticoagulation with a VKA were randomized to either clopidogrel plus aspirin or clopidogrel without aspirin.[12] The results showed that the use of clopidogrel without aspirin was associated with significantly fewer bleeding events without an apparent increase in ischemic events. WOEST was a pilot study with 573 participants from 2 countries and included indications for oral anticoagulation other than AF, so results did not lead to substantial changes in clinical practice guidelines. Nevertheless, WOEST represents the first challenge to the accepted paradigm that aspirin must be a cornerstone of therapy in patients with concomitant AF and CAD. Current guideline recommendations are mostly based on expert consensus, and the choice and duration of triple therapy depend on patient bleeding risk, stroke risk, and clinical presentation (ACS or elective PCI).[13-15]

Whereas WOEST used a VKA-based antithrombotic strategy, 2 subsequent trials have evaluated strategies using the non-VKA oral anticoagulants (NOACs) rivaroxaban and dabigatran. PIONEER AF-PCI randomized 2,100 patients with AF undergoing PCI to 1 of 3 antithrombotic therapy strategies: (1) rivaroxaban 15 mg daily with a P2Y12 inhibitor; (2) rivaroxaban 2.5 mg twice daily with aspirin and a P2Y12 inhibitor and transitioning to rivaroxaban 15 mg daily and aspirin when the P2Y12 inhibitor was stopped; or (3) VKA, aspirin, and a P2Y12 inhibitor and transitioning to VKA and aspirin when the P2Y12 inhibitor was stopped.[16] The trial demonstrated significantly less bleeding with each of the reduced-dose rivaroxaban-based antithrombotic strategies than with the VKA strategy, and there was no apparent difference in ischemic events, stroke, or stent thrombosis among the 3 treatment strategies.

The RE-DUAL PCI trial randomized 2,725 patients with AF undergoing PCI to 1 of 3 antithrombotic therapy strategies: (1) dabigatran 150 mg twice daily with a P2Y12 inhibitor; (2) dabigatran 110 mg twice daily with a P2Y12 inhibitor; or (3) VKA, P2Y12 inhibitor, and aspirin for 1 month in those receiving a bare metal stent or 3 months in those receiving a drug-eluting stent.[17] The trial demonstrated significantly less major or clinically relevant nonmajor (CRNM) bleeding (defined by the International Society on Thrombosis and Haemostasis [ISTH]) with each of the dabigatran-based antithrombotic strategies than with the VKA strategy. Although there were no statistically significant differences in ischemic events, stroke, or stent thrombosis, the low-dose dabigatran regimen of 110 mg twice daily was associated with numerically higher rates of stent thrombosis and myocardial infarction (MI). Although these trials were important, they were not powered or designed to assess whether the bleeding reduction was due to the use of a NOAC or due to the removal of aspirin from the post-PCI oral antithrombotic strategy. Additionally, in both studies, lower doses of NOACs were associated with numerically higher rates of ischemic events.

Rationale for apixaban

In the randomized, double-blind Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban 5 mg twice daily was compared with warfarin titrated to an international normalized ratio (INR) of 2.0 to 3.0 to prevent stroke and systemic embolism in 18,201 patients with AF.[18,19] The rate of the primary outcome was 1.27% for the apixaban arm versus 1.60% for the warfarin arm (hazard ratio [HR] 0.79, 95% CI 0.66-0.95; $P < .001$ for noninferiority; $P = .01$ for superiority). Although the ARISTOTLE study clearly demonstrated that apixaban 5 mg twice daily was associated with lower rates of bleeding and better efficacy than warfarin with an INR target of 2.0 to 3.0 in the overall AF study population, there was limited experience with patients who were also on DAPT. Patients were excluded from entry into ARISTOTLE if they were on DAPT at the time of randomization, but if a need for DAPT arose during the trial, this was allowed at the discretion of the investigator. Use of a single antiplatelet therapy, predominantly aspirin, was allowed both at initiation and during the trial. Aspirin use at baseline was associated with higher major and CRNM bleeding rates for both apixaban and warfarin without any significant association with ischemic events.[20]

In the Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) study, apixaban was compared with placebo in a patient population with ACS without an indication for oral anticoagulation predominantly receiving aspirin or aspirin plus clopidogrel.[21] This trial was stopped early because of an increase in major bleeding without a substantial concomitant reduction in ischemic events. In addition, the APPRAISE-2 trial included very few participants who had documented AF with their index ACS event, and the study specifically excluded those patients already on or with a formal indication for chronic oral anticoagulation.

The optimal treatment of patients with AF who require oral anticoagulation and develop ACS and/or undergo PCI remains uncertain. In such circumstances where oral anticoagulation therapy is required to prevent stroke and systemic embolism and concomitant antiplatelet therapy is required to minimize the risk of recurrent ischemic events or stent thrombosis, major bleeding remains a serious concern. The use of NOACs appears to offer a number of advantages compared with VKA therapy, including the potential for less bleeding; however, additional randomized trial data are needed, especially regarding the discontinuation of aspirin from the treatment strategy of these patients.

Methods

The Open-Label, 2 × 2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention (AUGUSTUS [NCT02415400]) is a large, prospective, multicenter, randomized trial with 2 main objectives: (1) to determine whether apixaban is noninferior to VKA (INR target range 2.0-3.0) for the combined end point of ISTH major and CRNM bleeding in patients with AF who develop ACS and/or undergo PCI with planned concomitant P2Y12 inhibitor therapy for at least 6 months and (2) to determine whether anticoagulant plus single antiplatelet therapy with a P2Y12 inhibitor for at least 6 months is superior to anticoagulant plus DAPT with a P2Y12 inhibitor for at least 6 months and aspirin on the combined outcome of ISTH major and CRNM bleeding in the same population.

The trial plans to enroll around 4,600 patients at approximately 500 sites in 33 countries. The first patient was randomized on September 1, 2015, and recruitment is planned to end in April 2018.

This trial is being conducted in compliance with the study protocol, the Declaration of Helsinki, and Good Clinical Practice, as defined by the International Conference on Harmonization. Prior to patient participation, written informed consent will be obtained from each patient, and approval will be obtained from appropriate ethics committees at participating sites.

Study population

Study entry criteria are summarized in Table I. Briefly, patients with AF and a recent ACS and/or those undergoing PCI with planned treatment with P2Y12 inhibitor for at least 6 months and oral anticoagulation will be evaluated for eligibility during their ACS and/or PCI hospitalization. Patients with other conditions that require anticoagulation (such as prosthetic valves or moderate or severe mitral stenosis), severe renal insufficiency, and history of intracranial hemorrhage will be excluded.

Table I
Key inclusion and exclusion criteria

Inclusion criteria	1. Must be ≥18 y of age (or age of majority) with either active or a history of AF or flutter with planned or existing use of an oral anticoagulant for prophylaxis of thromboembolism 2. Must have had an ACS (STEMI, NSTEMI, or unstable angina) AND/OR a PCI within the prior 14 d 3. Planned use of an approved P2Y12 inhibitor for at least 6 m
Exclusion criteria	1. Conditions other than AF that require chronic anticoagulation (eg, prosthetic mechanical heart valve, DVT, or PE) 2. Severe renal insufficiency (serum creatinine >2.5 [221 μmol/L] or a calculated CrCl <30 mL/min 3. Patients with any history of intracranial hemorrhage 4. Any contraindications to VKA, apixaban, intended P2Y12 inhibitors, or aspirin 5. Recent or planned CABG surgery for the index ACS event 6. Patients with known ongoing bleeding 7. Patients with known coagulopathies

STEMI, ST-segment elevation myocardial infarction; *NSTEMI*, non–ST-segment elevation myocardial infarction; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *CrCl*, creatinine clearance; *CABG*, coronary artery bypass graft.

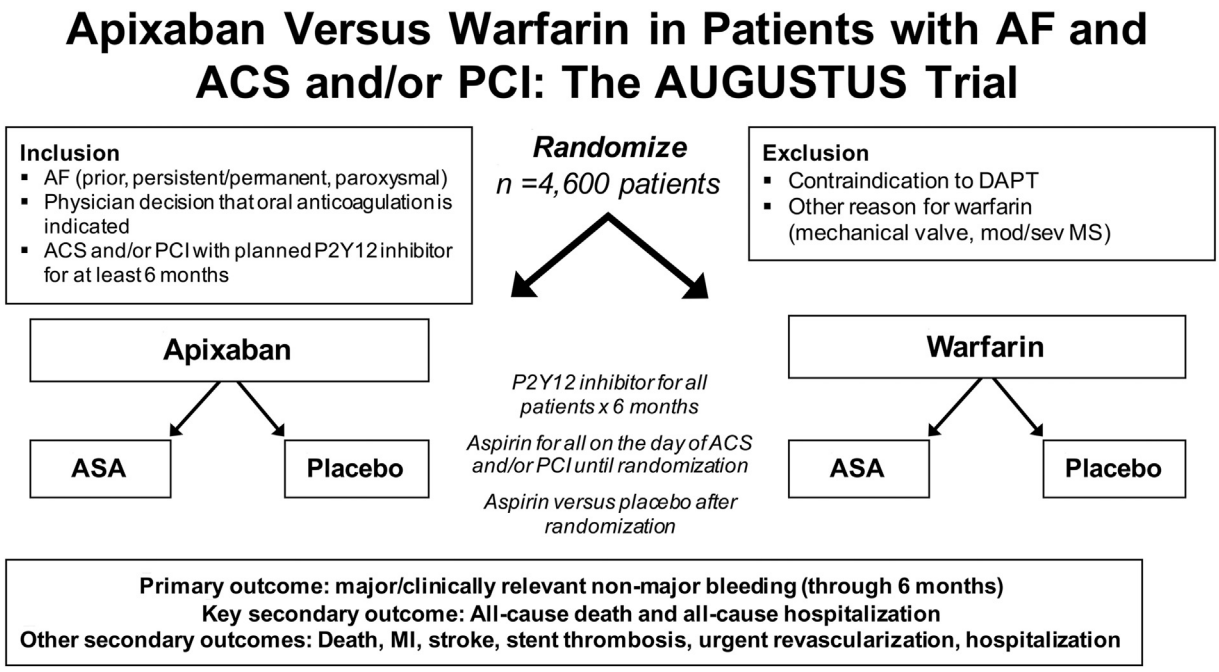

Figure 1. AUGUSTUS trial design.

Randomization and treatment

The trial schema is shown in Figure 1. Randomization will be performed up to 14 days after the ACS and/or PCI and should take place as early as possible after cessation of parenteral anticoagulant and when the patient is clinically stable. The 14-day window was provided to take into account worldwide variations in care of this patient population, although explicit guidance is provided to enroll and randomize patients as quickly as possible after the index event once parenteral anticoagulants have been stopped. Patients with or without prior oral anticoagulant treatment can be included. Patients who are on a VKA prior to randomization will have VKA discontinued and will not be dosed with apixaban until the INR is less than 2.0.

At enrollment, eligible patients will be randomized via an interactive voice response system using a 2×2 factorial design to either apixaban or VKA and to either aspirin or aspirin placebo. Randomization will be stratified by indication at enrollment (ACS vs PCI). Apixaban or VKA will be given in an open-label manner, whereas aspirin (or matching placebo) will be double-blinded. Participants randomized to apixaban will be dosed at 5 mg twice daily unless they meet ≥2 of the following criteria for the reduced dose of 2.5 mg twice daily: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥1.5 mg/dL (133 μmol/L). Participants randomized to VKA should be titrated up for an INR target goal of 2.0 to 3.0. Dosage of VKA to achieve that range should be per local standards of care and per investigator clinical judgment. Patients who take aspirin prior to randomization will switch to 81 mg aspirin or matching placebo. Both the oral anticoagulant (apixaban or VKA) and the antiplatelet agents (blinded aspirin once daily or blinded placebo once daily) must be started within 24 hours of randomization. During the 6-month treatment period with VKA or apixaban, other oral or parenteral anticoagulants (such as dabigatran, rivaroxaban, edoxaban, fondaparinux, unfractionated heparin, or low–molecular weight heparins) may not be given concurrently. The 6-month time window for follow-up, with an additional month for safety monitoring, was chosen because this is the primary period during which the risk of recurrent ischemic events is highest and must be weighed against bleeding risk. Additionally, with more recent guidance recommending shorter DAPT in patients receiving the latest-generation drug-eluting stents and the known risks of prolonged triple antithrombotic therapy, a longer duration of follow-up would lead to more patients discontinuing their P2Y12 inhibitor during the follow-up period.

Study outcomes

Primary outcomes

The primary outcome will be time to first occurrence of ISTH major or CRNM bleeding during the treatment period for the comparison between apixaban and VKA and for the comparison between aspirin and

Table II
Clinical events definitions

ISTH	A. Major bleeding Clinically overt bleeding that is associated with: • Death (fatal bleeding) or • Occurs in a critical area or organ or o Intracranial, o Intraspinal, o Intraocular, o Retroperitoneal, o Intraarticular, o Intramuscular with compartment syndrome o Pericardial • Transfusion of ≥2 U of PRBC or whole blood • Fall in hemoglobin of ≥2 g/dL B. Clinically relevant nonmajor bleeding Any overt bleeding that meets 1 or more of the following criteria: • Requires hospitalization • Requires a physician-guided medical or surgical intervention to treat the bleeding or results in unscheduled contact with a physician (visit or telephone call) or pain or impairment of daily activities • Results in a physician-guided change in antithrombotic therapy C. Minimal bleeding All other overt bleeding events that do not meet the criteria for a major bleeding event or clinically relevant nonmajor bleeding event.
Stroke	*Stroke* is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction that is not due to an identifiable nonvascular cause (ie, brain tumor, trauma, brain procedures, metabolic condition) that is: 1. Not reversible within 24 h or results in death (in <24 h) or 2. Resolves in <24 h and is accompanied by clear evidence of a new stroke on cerebral imagingAll strokes will be classified as ischemic, hemorrhagic, or undetermined.
MI	*Acute MI* refers to evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. 1. Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least 1 value above the URL and with at least 1 of the following: • Symptoms of ischemia • New or presumed new significant ST-segment T-wave changes or new LBBB • Development of pathological Q waves in the ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality • Identification of an intracoronary thrombus by angiography or autopsy 2. Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained or before cardiac biomarker values would be increased. 3. *PPCI-related MI* is defined by elevation of cTn values (>5× URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, at least 1 of the following is required: • Symptoms suggestive of myocardial ischemia • New ischemic ECG changes • Angiographic findings consistent with a procedural complication • Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality 4. Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of evidence of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least 1 value above the 99th percentile URL 5. *CABG-related MI* is defined by elevation of troponin values (>10× URL) in patients with normal baseline cTn values (≤URL). In addition, at least 1 of the following is required: • New pathological Q waves or new LBBB • Angiographically documented new graft or new native coronary artery occlusion • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Cardiac troponin is the preferred biomarker for diagnosis of MI. In the absence of troponin, CK-MB will be used.
Stent thrombosis	Stent thrombosis will be classified as acute, subacute, late, and very late stent thrombosis. Stent thrombosis categories include: • Definite stent thrombosis • Probable stent thrombosis • Possible stent thrombosis
Death	All deaths will be categorized as cardiovascular, noncardiovascular, or undetermined In addition, all deaths will further be subclassified based on specific cardiovascular and noncardiovascular categories.

PRBC, packed red blood cells; *cTn*, cardiac troponin; *URL*, upper reference limit; *LBBB*, left bundle-branch block; *ECG*, electrocardiograph; *CK*, creatine kinase.

placebo. *ISTH major bleeding* is defined as clinically overt bleeding with a hemoglobin drop of at least 2 g/dL or transfusion of ≥2 U of packed red cells, or bleeding occurring at a critical site or resulting in death. *CRNM bleeding* is defined as any overt bleeding that does not meet criteria for major bleeding and meets 1 or more of the following criteria: requires hospitalization; requires a physician-guided medical or surgical intervention to treat the bleeding, or results in unscheduled contact with a physician (visit or telephone call), or results in pain or impairment of daily activities; or results in a physician-guided change in antithrombotic therapy. Outcomes will be adjudicated according to standard definitions by an independent committee blinded to treatment assignment (Table II).

Secondary outcomes

Secondary outcomes for the comparison of apixaban with VKA include superiority for the outcomes of ISTH major or CRNM bleeding; the composite end point of all-cause death and all-cause hospitalization; the composite end point of all-cause death, stroke, MI, stent thrombosis, and urgent revascularization; and first hospitalization for any cause. A key prespecified secondary outcome is the composite of all-cause death and all-cause hospitalization. Secondary outcomes for the comparison of aspirin versus placebo include the composite end point of all-cause death, stroke, MI, stent thrombosis, and urgent revascularization and first hospitalization for any cause. A prespecified secondary outcome for the comparison of aspirin with placebo is the composite of all-cause death and all-cause hospitalization.

Exploratory outcomes

Exploratory outcomes for the comparison of apixaban with VKA and for aspirin with placebo include ISTH major bleeding, net clinical benefit (composite of all-cause death/ischemic events and major bleeding), all-cause death, cardiovascular death, MI, stroke, stent thrombosis, urgent revascularization, and all-cause hospitalization.

Sample size calculation and statistical analysis

This study is designed to evaluate 2 safety hypotheses in patients with AF with recent ACS and/or PCI: (1) apixaban is noninferior to VKA for the combined outcome of ISTH major and/or CRNM bleeding, and (2) single antiplatelet therapy with a P2Y12 inhibitor is superior to DAPT with a P2Y12 inhibitor and aspirin for the combined outcome of ISTH major and/or CRNM bleeding.

A total of 357 primary end point events in 4,600 participants will provide 77% power for the test of noninferiority using a stratified log-rank test of apixaban compared with VKA, assuming a noninferiority margin of 1.2, with major or CRNM bleeding event rates in the apixaban and VKA groups of 8.1% and 9% per half year, respectively; a 1-sided significance level of .025; and 6-month follow-up and 1% per year of loss to follow-up. The noninferiority margin was selected because an absolute risk difference of 1.8% (20% of VKA event rate of 9%) in bleeding is considered to be a clinically meaningful difference. This sample size will also provide at least 77.5% power for superiority testing of apixaban compared with VKA, assuming a risk reduction of 25% and a 2-sided significance level of .05.

A blinded assessment of the primary outcome event rate will be performed after 50% of participants have completed the study. The analysis will focus on the aggregate event rate, and the sample size may be increased if the aggregate event rate is lower than anticipated. The sample size may be adjusted (depending on availability of resources) to provide sufficient power for both noninferiority and superiority testing of the primary outcome between apixaban and VKA.

The primary safety data set will consist of all patients who receive at least 1 dose of study drug. A secondary data set, the evaluable patient data set, will exclude data from those with protocol deviations expected to affect the primary safety outcome. For the primary safety outcome, analyses will be performed using the evaluable patient data set as well as the primary safety data set. For other safety outcomes, analyses will be performed using the primary safety data set. For the efficacy outcomes, analyses will be performed using data from all randomized patients regardless of the treatment actually received.

Comparisons between apixaban and VKA

A hierarchical testing strategy will be used to compare the effects between apixaban and VKA treatment groups. Noninferiority for the primary safety outcome of ISTH major or CRNM bleeding will be tested first at a 1-sided $\alpha = .025$. If noninferiority for the primary safety outcome (using a noninferiority margin of 1.2) is not demonstrated, then stop.

If noninferiority for the primary safety outcome is demonstrated, then superiority for the primary safety outcome will be tested at a 1-sided $\alpha = .025$; and in parallel, the superiority for the composite outcome of all-cause death and all-cause hospitalization will be tested at a 1-sided $\alpha = .025$ without type I error rate adjustment, as the 2 end points serve different purposes. The bleeding outcome will be used to evaluate the safety of apixaban, and the efficacy outcome will be used to demonstrate the effectiveness of apixaban. If the superiority for the composite outcome of all-cause death and all-cause hospitalization is not demonstrated, then stop.

If the superiority for the composite outcome of all-cause death and all-cause re-hospitalization is demonstrated, then superiority for the composite outcome of death and ischemic events will be tested at a 1-sided $\alpha = .025$. If the superiority is not demonstrated, then stop.

If the superiority is demonstrated, then superiority for time to first hospitalization for all-cause hospitalization will be tested at a 1-sided $\alpha = .025$.

The analysis of the primary safety outcome will be performed using a Cox proportional-hazards model including treatment group as a covariate and stratified by indication at enrollment (nonemergent PCI or ACS) and antiplatelet use (aspirin placebo or aspirin). A point estimate and 2-sided 95% CI for HRs and a *P* value for the test of equality of rates (HR = 1) will be calculated. Noninferiority will be demonstrated if the upper bound of the 2-sided 95% CI for the HR is less than 1.2.

Event rates for the exploratory outcomes will be summarized by apixaban and VKA treatment group. Point estimates and 2-sided 95% CIs for HRs will be constructed for the outcome using the methods described for the primary outcome, and nominal *P* values will also be provided.

Comparisons between aspirin and aspirin placebo

Although no formal statistical testing will be performed for the comparisons between aspirin- and placebo-treated groups, analyses for the primary, secondary, and other outcomes will be reported (similar to that done for the apixaban and VKA comparison) but with nominal *P* values. The statistical framework of the trial, including the sample size calculation, was designed for the apixaban and VKA comparison.

Clinical events classification committee

Clinical events classification of all end points will be led by the Duke Clinical Research Institute (DCRI) (Durham, NC). All suspected death, MI, unstable angina, stroke, transient ischemic attack, bleeding events, and stent thrombosis will be adjudicated in a blinded manner. Causes of hospitalization will be classified as cardiovascular, bleeding, or other. Each potential event will be adjudicated by 2 physicians, and disagreements will be reviewed by a physician committee. The adjudicating members of the DCRI Clinical Events Classification group will remain blinded to all treatment assignments (including the open-label apixaban vs VKA arm) throughout the adjudication process and the duration of the trial. Event definitions are provided in Table II.

Executive, steering, and data safety monitoring committees

The AUGUSTUS executive committee is led by the DCRI and oversees the design, execution, analysis, and reporting of the study. This committee will convene regularly to address policy issues and monitor study progress, execution, and management. The steering committee comprises the national leaders from each participating country and will meet periodically to discuss the progress of the study. All primary and secondary analyses of this study will be performed and led by the DCRI.

An independent data monitoring committee, composed of 2 cardiologists and 1 statistician, will review serious adverse events, adverse drug effects, and primary outcome data on a 6-month basis and report to the executive committee.

There will not be a formal interim analysis during the trial, thus no intention to "spend" α prior to the final analysis and no intention to stop the trial early for futility or for benefit.

The data monitoring committee may recommend termination of the study for a safety concern that is assessed to outweigh potential benefits.

Taking into consideration the totality of both bleeding and ischemic event data, the data monitoring committee may recommend stopping enrollment and study drug in an arm (or cell) if there is reasonable evidence that a standard-of-care arm or cell (VKA or aspirin) is superior to a non–standard-of-care arm or cell (apixaban or aspirin placebo) or if there is proof beyond a reasonable doubt that a non–standard-of-care arm or cell (apixaban or aspirin placebo) is superior to a standard-of-care arm or cell (VKA or aspirin). Although no constraining quantitative guidelines are outlined in the data monitoring committee charter, there are broad outlines for recommending the discontinuation of any cell or randomization arm of the study for either safety or futility.

Depending on the observed results, the data monitoring committee could recommend continuing the trial as designed or stopping the entire trial, or 1 entire arm (all apixaban, all VKA, all aspirin, or all aspirin placebo), or 1 single cell (apixaban/aspirin, VKA/aspirin, apixaban/aspirin placebo, or VKA/placebo). If an arm or cell is stopped, additional patient participants may be randomized into the remaining arms or cells at the discretion of the executive committee and sponsor.

AUGUSTUS is sponsored by Bristol-Myers Squibb and Pfizer.

Discussion

Apixaban was superior to warfarin for the prevention of stroke or systemic embolism in patients with AF and was associated with lower rates of bleeding.[19] However, little data are available to inform its use in patients with AF who require concomitant DAPT. Pivotal NOAC trials in AF excluded patients needing DAPT, whereas DAPT trials following acute MI and/or PCI excluded patients on oral anticoagulation.[19,21-27] AUGUSTUS will help answer important questions about patients with AF and CAD and has some unique features. First, it is the largest study in the field, including the whole spectrum of patients with CAD (ACS with or without PCI, and elective PCI). Second, the apixaban dose (5 mg twice daily) used in AUGUSTUS has proven efficacy in stroke prevention in AF. Third, the unique 2×2 factorial design will provide insight into whether aspirin may (or may not) be dropped in patients with AF and CAD receiving oral anticoagulation plus a P2Y12 inhibitor. Fourth, unlike PIONEER AF-PCI and RE-DUAL PCI, AUGUSTUS does not exclude patients with a history of prior stroke, transient ischemic attack, prior gastrointestinal bleeding, or anemia. Finally, the 6-month follow-up will delineate bleeding and ischemic events in the highest-risk time period following the index event. Because the most recent guidelines provide a class I indication for DAPT in stable ischemic patients treated with current drug-eluting stents for 6 months only, patients will not be subjected to the prolonged DAPT that was used for those receiving prior-generation drug-eluting stents.[14] Moreover, patients may be enrolled within 14 days of the index event (ACS and/or PCI), whereas in other trials, this time frame was shorter (3-5 days). This will allow more time before randomization for patients to be treated at the discretion of their physician with any antithrombotic strategy until they are stable.

In AUGUSTUS, the patient population will include both patients with new-onset AF as well as those already on a stable anticoagulant regimen. Permissible baseline anticoagulants at study entry include any VKA as well as any NOAC, including factor Xa inhibitors or thrombin inhibitors. Patients already on oral anticoagulants before randomization will have the original anticoagulants stopped in accordance with their labeling prior to randomization and will be transitioned to either VKA or apixaban.

The 5-mg twice-daily dose of apixaban was chosen because of proven efficacy for stroke reduction compared with warfarin in patients with AF. This dose was associated with increased bleeding compared with placebo in the APPRAISE-2 trial. In AUGUSTUS, however, we are comparing apixaban with warfarin. In ARISTOTLE, this same dose of apixaban was associated with a 31% reduction in major bleeding compared with warfarin. Thus, we believe that apixaban 5 mg twice daily is the most appropriate dose to be tested in AUGUSTUS to assess efficacy, safety, and clinical outcomes in this trial population.

The PIONEER AF-PCI trial provided initial evidence regarding the optimal antithrombotic strategy for patients with AF and concomitant coronary disease.[16] Although a clear signal of fewer bleeding events was observed with both regimens including rivaroxaban, the efficacy outcome (death from cardiovascular causes, MI, and stroke) occurred at similar rates among treatment arms. This bleeding reduction was observed using doses of rivaroxaban that have not demonstrated proven efficacy in stroke reduction among patients with AF. Furthermore, the point estimates for ischemic events were concerning for increased risk of events, although this study was not powered for efficacy and effects on ischemic events were imprecise because of wide CIs.

The findings of the RE-DUAL PCI trial[17] generally mirrored those from PIONEER AF-PCI in that the study demonstrated a reduction in bleeding in the NOAC arms compared with the traditional VKA-based triple-therapy arm. It also confirmed the baseline bleeding risk among patients treated with triple therapy. However, RE-DUAL PCI was unable to provide insight into whether the reduction in bleeding in the dabigatran-based arms was due to treatment with dabigatran or the removal of aspirin. Additionally, the trial tested a dose of dabigatran (110 mg twice daily) that is unavailable in the United States, although treatment at this dose demonstrated a trend toward an increased risk of MI (HR 1.51, 95% CI 0.94–2.41; $P = .09$) and definite stent thrombosis (HR 1.89, 95% CI 0.79–4.40; $P = .15$) when compared with the corresponding triple-therapy group.

Two other trials of antithrombotic therapy strategies among patients with AF requiring DAPT are ongoing. The Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF PCI) trial[28] will randomize 1,500 patients with a history of AF to an edoxaban-based strategy or VKA on top of aspirin and a P2Y12 inhibitor. The study will enroll patients outside the United States, and results are expected in 2019. SAFE A[29] will randomize 600 patients with AF undergoing PCI with a drug-eluting stent to 1 month or 6 months of P2Y12 inhibitor therapy on background apixaban and aspirin, providing guidance on the optimal duration of an apixaban-based triple-therapy regimen. The primary outcome for both trials will be ISTH major or CRNM bleeding at 1 year.

The field of combination antiplatelet and anticoagulant therapy in high-risk patients is evolving rapidly, and PIONEER AF-PCI and RE-DUAL PCI provided important randomized data where prior experience was limited. Nevertheless, AUGUSTUS will extend the findings of those trials in important ways and will be the first large randomized study to test the WOEST strategy and distinguish the bleeding contributions of apixaban and the removal of aspirin. The trial will provide unique information that will inform physicians and guidelines on the optimal antithrombotic strategy in these high-risk patients across the spectrum of CAD.

Conclusion

AUGUSTUS is the largest trial to date in patients with AF and coronary disease, including those with ACS and/or undergoing PCI, comparing apixaban with VKAs as well as aspirin with placebo in patients receiving a P2Y12 inhibitor for at least 6 months. The unique features of this study, including the 2 × 2 factorial design, blinded aspirin/placebo comparison, and the inclusion of the entire spectrum of patients with coronary disease, will add to the body of evidence to guide the selection of the optimal antithrombotic regimen for this challenging group of patients.

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