Polypharmacy and the effects of apixaban in patients with atrial fibrillation: insights from the ARISTOTLE trial

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Complete List of Authors:	Jaspers Focks, Jeroen; Radboud University Medical Center, Cardiology Brouwer, Marc; Radboud University Medical Center, Department of Cardiology Wojdyla, daniel; Duke Clinical Research Institute, Thomas, Laine; Duke Clinical Research Institute, Lopes, Renato; Duke Clinical Research Institute Washam, Jeffrey; Duke Heart Center, Duke University Medical Center Lanas, Fernando; Universidad de La Frontera, Internal Medicine Xavier, Denis; St Johns Medical College and Research Institute, Pharmacology and CLinical Trials Husted, Steen; Hospital Unit West, Medical Department Wallentin, Lars; Uppsala Clinical research centre Sweden Alexander, John; Duke Clinical Research Institute, Granger, Christopher; Duke Clinical Research Institute, Verheugt, Freek; Radboud University Medical Center, Department of Cardiology
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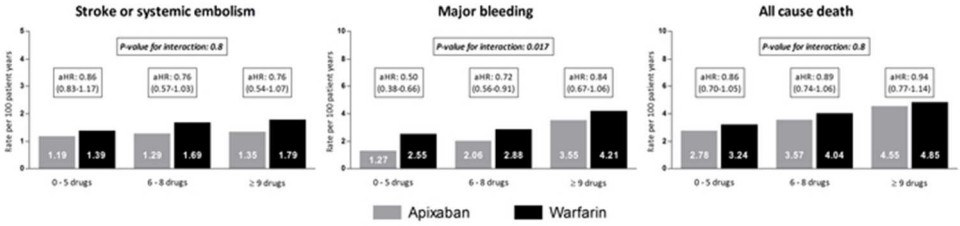

Figure 1
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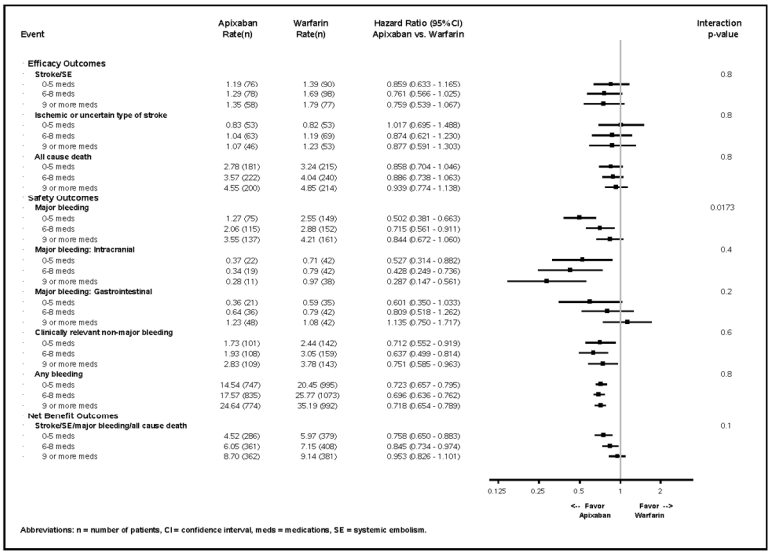

Figure 2
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Polypharmacy and the effects of apixaban in patients with atrial fibrillation: a post-hoc analysis of the ARISTOTLE trial

Jeroen Jaspers Focks, *Research fellow*[1], Marc A. Brouwer, *Director of research and cardiologist*[1], Daniel M. Wojdyla, *Biostatistician*[2], Laine Thomas, *Biostatistician*[2], Renato D. Lopes, *Associate Professor of Medicine, Cardiology*[2], Jeffrey B. Washam, *Clinical Pharmacist*[3], Fernando Lanas, *Professor of Medicine*[4], Denis Xavier, *Professor and Head, Department of Pharmacology*[5], Steen Husted, *Clinical Associate Professor*[6], Lars Wallentin, *Senior Professor of Cardiology*[7], John H. Alexander, *Professor of Medicine, Cardiology*[2], Christopher B. Granger, *Professor of Medicine, Cardiology*[2], Freek W.A. Verheugt, *Senior Professor of Cardiology*[1]

[1]Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands; [2]Duke Clinical Research Institute, [3]Duke Heart Center, Duke University Medical Center, Durham, NC, USA; [4]Department of Cardiology, Universidad de La Frontera, Chile; [5]Department of Pharmacology and Clinical Research, St. John's Medical College and Research Institute, Bangalore, India; [6]Department of Medicine, Hospital Unit West, Herning, Denmark; [7]Department of Medical Sciences, Cardiology, Uppsala Clinical Research Center, Uppsala, Sweden.

Address for correspondence: Jeroen Jaspers Focks, MD, Department of Cardiology, Radboud University Nijmegen Medical Center, PO Box 9101, Internal code: cardiology 616, 6500 HB Nijmegen, The Netherlands. Phone: +31-24-3616785; Fax: +31-24-3635111. Email: Jeroen.Jaspersfocks@radboudumc.nl.

Abstract

Objective: In various clinical settings, polypharmacy has been associated with frailty and adverse outcome. Compared with warfarin, apixaban has a superior efficacy and safety profile in atrial fibrillation. However, patients with polypharmacy may have a differential response to anticoagulation therapy, due to extensive comorbidity and/or drug-drug interactions.

Design, Participants, Interventions, Main Outcome Measures: Patients in the ARISTOTLE trial (n=18,201) were divided into tertiles according to the number of medications used at baseline. We compared clinical outcomes and the treatment effects of apixaban versus warfarin (adjusted for age, sex, and country).

Results: Patients used a median of 6 drugs (interquartile range 5 to 9); polypharmacy (≥5 drugs) was seen in 76%. Greater numbers of concomitant medications were used in older patients and in women, and in patients in the United States. Number of comorbidities increased across tertiles of increasing number of medications (0-5; 6-8; ≥9 drugs), as did the proportions of patients with drugs that interact with warfarin or apixaban. Mortality significantly increased as number of medications increased. Across tertiles of increasing numbers of drugs, rates of stroke/systemic embolism (1.29; 1.48; 1.57 per 100 patient-years, respectively) and major bleeding (1.91; 2.46; 3.88 per 100 patient-years, respectively) increased. The relative risk reductions of stroke or systemic embolism for apixaban versus warfarin were consistent, regardless of the number of concomitant medications (interaction p-value=0.8). With regard to major bleeding, there was less reduction seen with apixaban versus warfarin with greater numbers of concomitant drugs (interaction p-value 0.017). Patients with interacting (potentiating) drugs for warfarin or apixaban had similar outcomes and consistent treatment effects of apixaban versus warfarin.

Conclusions: In ARISTOTLE, three quarters of patients have polypharmacy, and they constitute a population with a greater comorbidity, more interacting drugs, increased mortality, and higher rates of thrombo-embolic and bleeding complications. In terms of a potential differential response to anticoagulation therapy in patients with AF and polypharmacy, apixaban was more effective than warfarin and at least as safe.

Trial Registration: ClinicalTrials.gov (NCT00412984).

Print abstract

Study question: Does the treatment effect of apixaban versus warfarin differ with increasing numbers of concomitant medications in patients with atrial fibrillation?

Methods: Patients in the ARISTOTLE trial (n=18,201, median follow-up 1.8 years) were divided into tertiles according to the number of medications used at baseline. We compared clinical outcomes and the treatment effects of apixaban versus warfarin (adjusted for age, sex, and country).

Study answer and limitations: With increasing numbers of drugs, co-morbidity increased, as did the risk of stroke and systemic embolism, major bleeding and mortality. Patients with polypharmacy (seen in 76%) were older and were more often from the United States. As for the benefit in efficacy of apixaban versus warfarin, relative risk reductions in stroke or systemic embolism were consistent (interaction p-value=0.8), regardless of the number of concomitant drugs. With regard to major bleeding, there was a decrease in the relative benefit of apixaban over warfarin with increasing numbers of co-medication (interaction p-value 0.017). The attenuation of the safety benefit was not explained by differences in use of interacting drugs, such as CYP3A4/P-gp inhibitors and warfarin potentiators. Although it is plausible that polypharmacy may cause a differential drug response to oral anticoagulation, this is a post-hoc analysis, on baseline burden of medication.

What this study adds: In this population of patients with atrial fibrillation, three quarters of patients have polypharmacy, and they constitute a population with a greater comorbidity, more interacting drugs, increased mortality, and higher rates of thrombo-embolic and bleeding complications. In terms of a potential differential response to anticoagulation therapy in patients with atrial fibrillation and polypharmacy, apixaban was more effective than warfarin and at least as safe.

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Trial Registration: ClinicalTrials.gov (NCT00412984).

Introduction

In an era of increasing life expectancy, and with a growing population of survivors with various comorbidities, clinical decision making with regard to antithrombotic therapy for atrial fibrillation (AF) has become an even greater clinical challenge.[1] Despite the often well appreciated risk of stroke, oral anticoagulation is often not prescribed in the elderly, and undertreatment has been associated with adverse outcome.[2,3] However, physicians increasingly acknowledge that treatment decisions should probably be based on biological rather than chronological age.[4]

In a variety of populations, polypharmacy has been associated with multiple comorbidities and frailty.[5-10] Moreover, the risk of drug-drug interactions increases with the number of concomitant drugs. In addition, polypharmacy has been related to a higher risk of death and bleeding complications, also in patients with AF.[6-17] In this context, patients with polypharmacy may have a differential response to anticoagulation therapy.

With the introduction of apixaban, a safer alternative to warfarin has become available which has also proven to be of value in patients considered unsuitable for warfarin.[18,19] In a previous report we demonstrated that the benefits of apixaban versus warfarin were irrespective of age (<65 yrs vs 65-74 yrs vs ≥75 yrs). However, among the elderly there are patients with hardly any comorbidity, whereas there are also younger patients with significant comorbidity. On average, patients with AF use about four to six different medications,.[10,11,20] Given that polypharmacy is generally defined as the use of five or more concomitant medications, and thus represents an everyday issue, additional information on the impact of oral anticoagulation drugs in this specific subset of patients is of clinical importance.[21] Especially in the case of apixaban, information on the impact of potentiating drugs is limited, an issue that is specifically of interest in patients with many concomitant drugs.

In this context, we performed a post-hoc analysis of the ARISTOTLE trial (Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation) to assess the association between the number of drugs used and the extent of comorbidity and adverse outcome.[19] In addition, we addressed the relative treatment effect of apixaban versus warfarin in relation to the number of concomitant medications.

Methods

Patients

The study design and the main outcomes of the ARISTOTLE trial have been reported previously.[19,22] In brief, ARISTOTLE was a multicenter double-blind, double-dummy trial comparing apixaban with warfarin. Patients with documented AF or atrial flutter were eligible for inclusion if one or more of the following risk factors for thromboembolism were present: symptomatic heart failure within 3 months prior to inclusion or left ventricular function ≤40%; hypertension requiring pharmacological treatment; age ≥75 years; diabetes mellitus; and prior stroke, transient ischemic attack (TIA), or systemic embolus. Exclusion criteria included clinically significant mitral stenosis, conditions other than AF requiring anticoagulation, required aspirin treatment in a dose >165 mg/day or used in combination with a thienopyridine, recent ischemic stroke, AF due to reversible causes, an increased bleeding risk considered to be a contraindication for oral anticoagulation, and severe renal insufficiency (i.e., serum creatinine >2.5 mg/dL or a calculated creatinine clearance <25 mL/min).

Patients were randomized to either apixaban 5 mg twice daily (n=9120) or warfarin (n=9081). The target international normalized ratio (INR) range was 2.0 to 3.0, using a blinded encrypted point of care device. In cases where two or more of the following three criteria were present at baseline, patients received apixaban in a dose of 2.5 mg twice daily or matching placebo: age ≥80 years, body weight ≤60 kilograms, serum creatinine ≥1.5 mg/dL. The study was approved by appropriate ethical committees at all sites and all patients provided written informed consent

Concomitant medications and comorbidity

To investigate the association between the number of concomitant medications and the extent of comorbidity, we assessed the number of drugs used for each patient. The study drug (apixaban or warfarin) and the matching placebo were counted as one drug. All medications were categorized according to the Anatomical Therapeutic Chemical classification system.[23] Polypharmacy was defined as the use of five or more concomitant drugs.[21]

The use of drugs known to interact with apixaban or warfarin was assessed for each patient. For apixaban, we studied drugs known to inhibit both the cytochrome P450 3A4 (CYP3A4) enzyme as well as the P-glycoprotein (P-gp) as depicted by the Food and Drug Administration (FDA).[24] For warfarin, we studied the use of drugs known to inhibit or potentiate its anticoagulant effect with a high probability according to the American College of Chest Physicians guideline.[25]

All analyses performed were based upon the baseline medication burden; only for the anticoagulant we also studied premature permanent study drug discontinuation and for patients assigned to warfarin we calculated the time in therapeutic range (TTR) according to the Rosendaal method.[26]

Per protocol, the use of any concomitant medications during the trial was left to the discretion of the treating physician. The following concomitant medications were prohibited in combination with the study medication: potent inhibitors of CYP3A4 (e.g., azole antifungals, macrolide antibiotics, protease inhibitors, and nefazadone), aspirin in a daily dose >165 mg, other anticoagulant agents (e.g., unfractionated heparin, low molecular weight heparin, direct thrombin inhibitors, pentasaccharides), and glycoprotein IIb/IIIa inhibitors. If these agents were used during trial participation, study medication was to be (temporarily) interrupted and restarted as soon as the prohibited medication was discontinued. In addition, during the trial it was advised to cautiously use aspirin in combination with a thienopyridine, chronic daily use of a non-steroid anti-inflammatory agent, and cytotoxic or myelosuppressive therapy.

Clinical outcomes

We assessed outcomes in relation to the number of concomitant medications used at the time of randomization, during a median follow-up of 1.8 years (25th, 75th percentiles: 1.3, 2.3 years). The primary efficacy outcome was stroke (i.e., abrupt onset of focal neurological symptoms lasting at least 24 hours), or a systemic embolism (i.e., symptoms suggestive of an acute loss of blood flow to a non-cerebral artery, supported by evidence of embolism from surgical specimens, autopsy, angiography, or other objective testing).

Key secondary efficacy outcomes included assessment of the type of stroke (ischemic, hemorrhagic, unspecified) and all-cause death.

The primary safety endpoint was major bleeding according to the criteria set by the International Society on Thrombosis and Haemostasis (ISTH), which includes any clinically overt bleeding event accompanied by one or more of the following: a hemoglobin drop of 2 g/dL or more over a 24-hour period, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site (i.e., intracranial, intra-spinal, intraocular, intra-articular, pericardial, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding.[27] Moreover, clinically relevant non-major bleeding events were monitored and were defined as all clinically overt bleeding not meeting the criteria of major bleeding though leading to either hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy.

The combined endpoint of 'net benefit' was defined as the combination of death, stroke, systemic embolism, and major bleeding.

Statistical analysis

Based on the tertiles of the distribution of the number of concomitant medications used at baseline, patients were classified in three groups. Comorbidities, organized by organ system, were summarized for the three groups, as well as other baseline characteristics. A similar approach was followed for the different drug classes. Data were depicted as means and standard deviations for continuous variables and frequencies and percentages for categorical variables. One-way ANOVA and chi-square tests were used to compare groups. Efficacy, safety, and net benefit endpoints were compared among the three groups using rates per 100 patient-years of follow-up and adjusted hazard ratios with 95% confidence intervals. Adjusted hazard ratios were derived using Cox regression models adjusting for sex and age and country of randomization. In these models, age was considered non-linear and included as a restricted cubic spline. The randomized treatment effect was assessed within each group (0–5, 6–8, ≥9 medications) using a Cox regression model to estimate hazard ratios for apixaban versus warfarin along with 95% confidence intervals. The homogeneity of the randomized treatment effect across groups was tested by adding interaction terms to the Cox regression model.

The proportional hazard assumption was evaluated using scaled Schoenfeld residuals and no clinically relevant departure from the assumption was observed. All the analyses performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Patient involvement

No patients were involved in designing the study, in assessing the burden of the intervention on patients, or in explicitly setting outcome measures; however, outcomes were chosen to reflect daily practice described in earlier studies.[28] Final study results of the ARISTOTLE trial were disseminated to study participants through their treating physicians.

Results

Baseline characteristics and comorbidity

Table 1 depicts baseline characteristics of the study population, categorized in tertiles by the number of drugs. The randomized treatment was well balanced across tertiles and no relevant differences between apixaban and warfarin was observed for any of the drug categories across the tertiles (Supplementary Table 1).

Patients using more medications were older, more often female, and less often warfarin-naïve at study entry (Table 1). The $CHADS_2$ and HAS-BLED scores increased across tertiles of increasing number of concomitant medications. With increasing number of medications the associated comorbidity increased significantly (Table 1).

Concomitant drugs - classification according to organ or system

The median number of medications used was 6 (25th, 75th percentiles: 5, 9) and polypharmacy was present in 13,932 (76.5%) patients (Supplementary Figure 1). There were marked regional differences in the number of medications used, with 53% of patients enrolled in North America using 9 or more medications (United States 58%; Canada 38%), compared with 10–21% for the other regions (Table 1). Although 4 or more organ systems with comorbidity was higher in the U.S. (43.3% in the U.S.

versus 20.5% in non-U.S. countries), the greater number of medications in the U.S. was observed regardless of the number of comorbidities.

Across tertiles of polypharmcy, the median number of represented drug classes increased from 2 (2, 3) for patients using 0–5 medications to 5 (4, 5) for patients using 9 or more medications (Table 2).

There were no relevant differences between apixaban and warfarin regarding the proportion of drug classes. For each of the respective drug classes the proportion of patients using one or more drugs increased significantly across tertiles.

For each of the tertiles, the number of represented drug classes was higher in the U.S. than in the non-U.S. population (Supplementary Table 2 A, B). Despite this difference in prescription pattern, there was a clear association between the number of concomitant drugs at baseline and the number of comorbidities, both for the U.S. and the non-U.S. populations.

Clinical outcomes according to the number of concomitant medications

Efficacy outcomes

With regard to the primary efficacy endpoint (stroke and systemic embolism), patients using more concomitant medications were at higher risk, with an increase in event rates from 1.29 for patients using 0–5 medications to 1.57 per 100 patient-years for patients using 9 or more medications ($p<0.001$; Table 3). For the secondary efficacy outcomes there was also a significant association with the number of concomitant medications, with a two-fold increased risk for all-cause death, when the highest tertile (≥9 medications) was compared with the lowest (0–5 medications) ($p<0.001$).

Safety outcomes

The risk of major bleeding for patients using 6–8 and 9 or more medications was significantly higher when compared with those using 0–5 medications (6–8 medications: adjusted HR 1.24, 95% CI 1.04 to 1.49; 9 or more drugs: adjusted HR 1.72, 95% CI 1.41 to 2.10; Table 3). When subdividing major bleeding according to the location, no significant difference across tertiles was observed for

intracranial bleeding (p=0.73), while the event rate for gastrointestinal bleeding significantly increased with a higher number of concomitant medications.

Net benefit outcome

With regard to the combined endpoint stroke, systemic embolism, major bleeding, and all-cause death, event rates increased across tertiles (5.24, 6.59, and 8.92 per 100 patient-years for 0–5, 6–8, and 9 or more medications, respectively, p<0.001). This was associated with an adjusted hazard ratio of 1.84 (95% CI 1.631 to 2.071) for patients using 9 or more medications when compared with those using 0–5.

Other outcomes

With increasing numbers of medications, the risk of permanent study drug discontinuation increased significantly (discontinuation rates 14.3, 15.0, and 17.4 per 100 patient-years at risk for 0–5, 6–8 and 9 or more drugs, respectively, p<0.001) (Table 3). Poor INR control during follow-up (i.e., TTR below 66%) was highest in the patients using 0–5 concomitant medications and decreased across tertiles (53.2%, 50.2%, and 44.9% for 0–5, 6–8, and 9 or more respectively, p<0.001) (Table 3).

Treatment effect

Figures 1 and 2 outline the treatment effect of apixaban when compared with warfarin for the different outcomes categorized by the number of medications used at baseline.

For the primary efficacy outcome, risk reductions of apixaban versus warfarin were consistent, irrespective of the number of medications used (p interaction=0.8), with lower event rates on apixaban for all tertiles. Also for the secondary efficacy outcomes, no significant interactions were observed.

With regard to major bleeding, relative risk reductions for apixaban versus warfarin decreased with increasing number of drugs (p interaction=0.017), corresponding with absolute reductions per 100 patient-years of 1.28 to 0.82 to 0.66 for the three respective categories (0–5, 6–8, and 9 or more drugs). For intracranial bleeding, the absolute benefit on apixaban showed a numeric increase across tertiles; this, in contrast to the numeric differences in major gastrointestinal bleeding observed between

treatment groups. With regard to the combined outcome of stroke, systemic embolism, major bleeding and all-cause death, we observed no significant interaction between treatment groups (p=0.1) Rates of permanent study drug discontinuation were lower for apixaban in all tertiles (p interaction=0.4).

Interacting drugs

The proportion of patients using an interacting drug increased across tertiles, both for CYP3A4/P-gp inhibiting as warfarin potentiating drugs. At least one combined inhibitor of both the CYP3A4 enzyme and P-gp was used by 20.9% of the apixaban users and 21.1% of patients on warfarin used VKA potentiating drugs. (Table 2). As for the concomitant use of aspirin, NSAID and/or prednisone, proportions were 13.8%, 31.7%, and 49.7%, respectively (p<0.001).

Rates of major bleeding did not significantly differ between patients with or without combined CYP3A4 and P-gp inhibitors (2.59 vs 2.61 per 100 patient-years, respectively; Table 4). Moreover, no significant interaction with the treatment allocation was observed (p=0.4). With regard to drugs known to potentiate warfarin, we also observed no difference in event rate of major bleeding (2.60 vs 2.61 per 100 patient-year for users and non-users, respectively).

Discussion

In this post-hoc analysis of the ARISTOTLE trial, we demonstrated that polypharmacy is seen in three quarters of AF patients and that the number of concomitant medications is associated with increased comorbidity. Prescription patterns differed across regions, with approximately twice the number of concomitant medications in the U.S. vs non-U.S. populations. Adverse clinical outcome occurred more frequently in patients treated with a higher number of concomitant medications. The benefits of apixaban in reducing stroke were preserved, regardless of the number of medications taken. In terms of safety, while the rates of major bleeding were consistently lower with apixaban, the magnitude of benefit with apixaban decreased with the number of concomitant medications.

Polypharmacy and adverse outcomes

AF is a disease of the elderly, who have a varying extent of comorbidity, and associated concomitant medication.[29] Previous studies reported rates of polypharmacy in about 60% of AF patients.[9,10] Various reports have demonstrated, for different clinical conditions, that polypharmacy is associated with increased comorbidity.[5-10] In addition, studies focusing on elderly populations have linked polypharmacy to adverse drug reactions, falls, disability, and frailty.[6-8] In this context, patients with polypharmacy may constitute a population with a differential response to oral anticoagulation. Although differences in prescription thresholds may affect the classification of patients in individual cases, several reports have repeatedly demonstrated on a group level that polypharmacy is associated with comorbidity and adverse outcome, also in AF populations.[6-17] Our findings of higher risks of bleeding, stroke and all-cause mortality with increasing numbers of drugs are in line with these previous observations.

Notably, this higher risk of adverse outcomes should be placed in the context of the association between the number of medications and comorbidities present at baseline, indicating a more frail status of patients with polypharmacy. If we were to adjust for these baseline differences, it is likely that the risk of adverse outcomes related to the number of medications would diminish. However, it is not our objective to study the association between polypharmacy and adverse outcomes independent of the baseline difference. On the contrary, we studied the number of concomitant medications as a marker of comorbidity/frailty and adverse outcome.

As such, we performed adjustments limited to age, sex, and country of randomization. The latter is of special importance given the differences in prescription patterns between countries, independent of differences in comorbidity. It is striking that in the U.S., there is more use of polypharmacy, not explained by more comorbidity.

Polypharmacy and treatment effect

Considering that patients with polypharmacy have a higher risk of adverse outcomes and multiple coexisting impairments, it is of special interest to study whether the main trial results of the ARISTOTLE study are consistent among patients using numerous concomitant medications. As far as the primary endpoint of stroke and systemic embolism is concerned, the 21% risk reduction of

apixaban when compared with warfarin in the complete population was consistent irrespective of the number of medications used.[19]

Overall, the use of apixaban was associated with a 31% risk reduction in major bleeding.[19] However, we observed a statistically significant treatment interaction with relative risk reductions of apixaban varying from 50% (0–5 medications) to 28% (6–8 medications) and 16% (≥9 medications), respectively. Importantly, the risk reduction of intracranial bleeding did not diminish with an increasing number of concomitant medications. Therefore, the fact that the relative benefit of apixaban over warfarin appears to diminish across tertiles is due to other types of major bleeds. For example, with increasing numbers of medications, the numeric difference in gastrointestinal bleedings shifts from a benefit for apixaban (0–5 medications) to no apparent difference (≥9 medications) between both oral anticoagulants.

In the ROCKET AF trial, with overall similar rates of major bleeding for rivaroxaban and warfarin, there was also a treatment interaction for major bleeding, in that the hazard ratio for major bleeding in patients using fewer medications (0–4) was lower (adjusted HR 0.69, 95% CI 0.51 to 0.94) than observed in the entire study population (HR 1.04, 95% CI 0.90 to 1.20).[10] As for mortality, there was no difference in treatment effect of rivaroxaban in patients with polypharmacy. In ARISTOTLE, apixaban reduced the risk of mortality by 11% when compared with warfarin in the main study, a risk reduction that was consistent regardless of the number of concomitant medications.[19]

In ARISTOTLE as well as in ROCKET AF, patients with polypharmacy were older.[10] Nonetheless, the relative reduction of both apixaban and rivaroxaban on major bleeding proved to be consistent across the different age groups in previously reported post-hoc analyses.[30,31] Importantly, this implies that our findings cannot be inferred to the 'elderly patient' in general. In fact, our findings are irrespective of age and sex, and refer to the group of patients, both younger and older, with multiple comorbidities and medications.

Possible explanations for the attenuation of the observed safety benefit of apixaban with increasing concomitant drugs include effects of comorbidity and drug-drug interactions, or the play of chance. We demonstrated that various co-existing diseases (COPD, gastrointestinal disease, renal impairment) were more frequent with increasing numbers of concomitant drugs. Of interest, given the

consistent risk reduction of apixaban for intracranial bleeding, the treatment interaction for major bleeding is related to other major bleeding. Risk factors for gastrointestinal bleeding complications (e.g., previous gastric ulcer, gastrointestinal surgery, dyspepsia, aspirin/prednisone/NSAID use) were more prevalent among patients with polypharmacy. In addition, other non-gastrointestinal risk factors for bleeding were also more often common in patients with more concomitant medications (e.g., older age, renal impairment, anemia, diabetes, and previous bleeding).[32]

Other aspects that may account for the decrease in benefit of apixaban in patients in the highest tertile are the higher rates of permanent discontinuation and higher proportion of patients who were VKA-naïve.[33] These differences may blunt the observed risk reduction of apixaban in this tertile. Finally, the better INR control in patients with ≥9 medications may have diminished bleeding rates on warfarin in this subgroup.[34,35]

As for drug-drug interactions, we specifically studied the impact of warfarin potentiating drugs and the combination of CYP3A4 and P-gp inhibitors, given the possibility of higher apixaban plasma concentrations with these agents. However, there was no evidence of differential treatment effect between apixaban and warfarin across tertiles of the number of concomitant drugs when accounting for warfarin potentiating or for apixaban potentiating drugs.

The abovementioned effects of non-vitamin K antagonist oral anticoagulants in patients with polypharmacy have also been studied in a pooled analysis of data in the setting of secondary prevention after a venous thromboembolism.[15] For major bleeding, there was no treatment interaction, when the safety of dabigatran versus warfarin was compared in patients with ≤3 or >3 concomitant medications. However, these patients are much younger and less fragile when compared with a patients with AF.

Interestingly, also in the field of symptomatic venous thromboembolism the issue of a potential different response to oral anticoagulation therapy in 'fragile' patients has been studied into more detail.[36] Of note, in this study, patients were considered to be 'fragile' if they were >75 years, had a low body weight (<50 kg), or had impaired renal function (creatinine clearance <50 mL/min). Although this certainly identifies patients at risk, incorporation of multiple comorbidities would allow for a more refined identification of frail patients within these specific subsets of patients.[37]

In summary, polypharmacy may be a marker of multi-morbidity and a predictor of adverse outcomes, and it may provide a first, general impression of a patients' frailty status. Future research on a differential response with oral anticoagulation therapy in patients with multi-morbidity may focus on incorporation of the key frailty criteria, for example the Fried criteria, which may help to identify a group of higher-risk patients that is often underrepresented in clinical trials.[38] This may be a group that deserves additional attention, as far as the generalizability of trial data is concerned, not only in the field of anticoagulation therapy, but also for other therapies.[39]

Limitations

There are several limitations of this study. First, this is a post-hoc analysis, though there was a prospective detailed analysis plan. Second, the analyses are based on baseline medication burden, without information on drug changes, reason and/or appropriateness of drug prescription. However, with polypharmacy that is often driven by chronic medical conditions, dramatic reductions in the number of drugs are not very likely. Third, although the number of drugs may not only be driven by the extent of comorbidity, but also by prescription patterns, we acknowledge that this may have affected classification on an individual level. However, on a group level the use of polypharmacy has repeatedly demonstrated to be a marker of the extent of comorbidity and associated with adverse outcome. The cut-off value of 5 or more drugs may be somewhat arbitrary, but has been used in many previous reports. Appreciating that three quarters of patients would qualify for polypharmacy according to this definition, our statistical approach was not arbitrary, but based on a common approach of dividing our data into tertiles to allow exploration of polypharmacy across categories that are sufficiently large to avoid the hazard of small subgroups.

Conclusions

In this population with atrial fibrillation on oral anticoagulation therapy, polypharmacy (≥5 drugs) is observed in three quarters of patients. The extent of comorbidity increased with greater numbers of concomitant drugs, which was irrespective of regional prescription patterns. Mortality, stroke and major bleeding were also more frequent with increasing numbers of drugs. As for a potential

differential response to anticoagulation therapy in this context, we observed that apixaban was superior to warfarin in terms of efficacy, regardless of the number of medications taken, whereas its magnitude of benefit on major bleeding decreased with higher numbers of concomitant medications. There were important differences in the comorbidity profile that could account for this, and it did not appear that warfarin or apixaban potentiating drugs (CYP3A4, P-gp inhibitors) explained this observed treatment interaction. In summary, apixaban is more effective than and at least as safe as warfarin in patients with AF, regardless of polypharmacy.

What is already known on this topic:

- Polypharmacy is associated with increased co-morbidity, frailty and drug-drug interactions, and has repeatedly been shown to be a marker of adverse clinical outcome. In this context, patients with polypharmacy could have a differential response to anticoagulation therapy.
- In a general atrial fibrillation population, apixaban has been shown to be a more effective and safer alternative than warfarin, but it has not been determined if this also holds true for patients using numerous concomitant medications.

What this study adds:

- In patients with AF, apixaban was more effective than warfarin regardless of the number of concomitant medications and, while the rates of major bleeding were consistently lower with apixaban, the magnitude of benefit with apixaban appeared to decrease with increasing number of concomitant medications**.**
- It does not appear that the specific use of warfarin or apixaban potentiating drugs accounts for this differential response to anticoagulation therapy with regard to major bleeding.

Author statements

Contributors: All authors (JJF, MAB, DMW, LT, RDL, JBW, FL, DX, SH, LW, JHA, CBG, and FWAV) made substantial contributions to the conception and design of the work; the acquisition, and interpretation of data for the work. DMW and LT conducted the data analysis. JJF, MAB, and FWAV drafted the work and all authors revised it critically for important intellectual content and approved of the final version for submission. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authorship

All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors meet the ICMJE's criteria for authorship and reviewed and approved the manuscript for submission.

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Competing Interests

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Ethical Approval: The ARISTOTLE study was approved by the appropriate ethics committees at all sites; all patients provided written informed consent.

Transparency Declaration

Jeroen Jaspers Focks affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Data Sharing

No additional data available.

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Figure Legends

Figure 1. Association between randomized treatment and the main outcomes by number of baseline medications.

Figure 2. Treatment comparisons for efficacy, safety and net benefit outcomes between apixaban and warfarin according to the number of baseline medications.

608

Table 1. Baseline Characteristics by Number of Medications Used

	Number of Medications			
Characteristic	**0-5 (N=6943)**	**6-8 (N=6502)**	**9 or more (N=4756)**	**p-value**
Age, mean (SD), yrs	68 (10)	69 (10)	71 (9)	<.0001
Male, no, (%)	4687 (67.5%)	4107 (63.2%)	2991 (62.9%)	<.0001
Weight, mean (SD), kg	81 (19)	84 (21)	89 (23)	<.0001
Body mass index, mean (SD), kg/m^2	28.2 (5.4)	29.5 (6.0)	30.7 (6.5)	<.0001
Prior use of Vitamin K antagonists for >30 days, no (%)	3555 (51.2%)	3656 (56.2%)	3190 (67.1%)	<.0001
Creatinine, mean (SD)	1.02 (0.24)	1.06 (0.28)	1.12 (0.32)	<.0001
Region of enrollment, no. (%)				<.0001
North America	736 (10.6%)	1353 (20.8%)	2385 (50.1%)	
Latin America	1809 (26.1%)	1306 (20.1%)	353 (7.4%)	
Europe	3128 (45.1%)	2811 (43.2%)	1404 (29.5%)	
Asia	1270 (18.3%)	1032 (15.9%)	614 (12.9%)	
HAS-BLED score, mean (SD)	1.45 (0.96)	1.77 (1.02)	2.25 (1.05)	<.0001
$CHADS_2$ score, mean (SD)	1.87 (1.02)	2.15 (1.08)	2.44 (1.17)	<.0001
$CHADS_2$ score, no (%)				
≤1	3093 (44.5%)	2057 (31.6%)	1033 (21.7%)	<.0001
2	2309 (33.3%)	2400 (36.9%)	1807 (38.0%)	
≥3	1541 (22.2%)	2045 (31.5%)	1916 (40.3%)	
Randomized group, no. (%)				0.1
Apixaban	3424 (49.3%)	3320 (51.1%)	2376 (50.0%)	
Warfarin	3519 (50.7%)	3182 (48.9%)	2380 (50.0%)	
Low dose apixaban/placebo (2.5 mg bid) received	253 (3.6%)	288 (4.4%)	290 (6.1%)	<.0001
Comorbidities organized by organ system, no. (%)				
Cardiovascular				
CAD	1795 (25.9%)	2184 (33.6%)	2063 (43.4%)	<.0001
Prior MI	564 (8.1%)	985 (15.2%)	1036 (21.8%)	<.0001
History of PCI/CABG	369 (5.3%)	815 (12.5%)	1292 (27.2%)	<.0001
Congestive Heart Failure within 3 Months	1931 (27.8%)	2194 (33.7%)	1416 (29.8%)	<.0001
At Least Moderate Valvular Heart Disease	926 (13.4%)	1192 (18.3%)	1116 (23.5%)	<.0001
Syncope in Last 5 years	258 (3.7%)	279 (4.3%)	322 (6.8%)	<.0001
Hypertension with Pharmacological Treatment	5844 (84.2%)	5762 (88.6%)	4310 (90.6%)	<.0001
PAD	193 (2.8%)	290 (4.5%)	401 (8.5%)	<.0001
Aortic Aneurysm	46 (0.7%)	84 (1.3%)	139 (3.0%)	<.0001
Neurological/Cerebrovascular				
Carotid Stenosis	54 (0.8%)	93 (1.4%)	190 (4.0%)	<.0001
TIA	302 (4.4%)	315 (4.8%)	337 (7.1%)	<.0001
Stroke	808 (11.6%)	750 (11.5%)	569 (12.0%)	0.8
Dementia	22 (0.4%)	29 (0.5%)	45 (1.0%)	<.0001
Epilepsy	22 (0.4%)	49 (0.8%)	41 (0.9%)	0.0006
Pulmonary				

Table 1. Baseline Characteristics by Number of Medications Used

	Number of Medications			
Characteristic	**0-5 (N=6943)**	**6-8 (N=6502)**	**9 or more (N=4756)**	**p-value**
COPD	435 (6.3%)	626 (9.7%)	889 (18.7%)	<.0001
Asthma	157 (2.3%)	250 (3.9%)	462 (9.7%)	<.0001
Sleep Apnea	145 (2.1%)	262 (4.0%)	606 (12.8%)	<.0001
Gastrointestinal				
Dyspepsia	374 (5.4%)	445 (6.9%)	556 (11.7%)	<.0001
GE Reflux Disease	315 (4.5%)	527 (8.1%)	1074 (22.6%)	<.0001
Peptic Ulcer Disease	383 (5.5%)	417 (6.4%)	406 (8.5%)	<.0001
GI Surgery	509 (7.3%)	606 (9.3%)	575 (12.1%)	<.0001
Chronic Liver Disease	190 (2.7%)	193 (3.0%)	121 (2.5%)	0.4
Endocrine				
Hypo/Hyperthyrodism	429 (6.2%)	733 (11.3%)	878 (18.5%)	<.0001
Diabetes	806 (11.6%)	1603 (24.7%)	2138 (45.0%)	<.0001
End organ Damage due to DM	75 (1.1%)	219 (3.4%)	459 (9.7%)	<.0001
Musculoskeletal				
Falls within 1 year	140 (2.3%)	215 (3.6%)	398 (8.8%)	<.0001
Previous Non-Traumatic Fracture	299 (4.3%)	339 (5.2%)	436 (9.2%)	<.0001
Osteoporosis	151 (2.2%)	298 (4.6%)	521 (11.0%)	<.0001
Renal				
Chronic Kidney Disease	434 (6.3%)	520 (8.0%)	553 (11.6%)	<.0001
Creatine Clearance < 50 mL/min	927 (13.4%)	1112 (17.2%)	970 (20.5%)	<.0001
Hematological				
History of Anemia	210 (3.0%)	359 (5.5%)	676 (14.2%)	<.0001
Thrombocytopenia (platelet at baseline < 150)	510 (7.6%)	467 (7.4%)	332 (7.2%)	0.8
Bleeding History	779 (11.2%)	1029 (15.8%)	1232 (25.9%)	<.0001
Number of organ systems affected (median, 25th-75th)	2, 1-3	2, 2-3	3, 2-4	<.0001

Subcategorization of all baseline characteristics per treatment allocation is presented in Supplementary Table 1.

Abbreviations: n = number of patients, sd = standard deviation, yrs = years, no = number, kg = kilogram, m = meter, CAD = coronary artery disease, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, PAD = peripheral artery disease, TIA = transient ischemic attack, COPD = chronic obstructive pulmonary disease, GE = gastroesophageal reflux disease, GI = gastrointestinal, DM = diabetes mellitus, mL = milliliter, min = minute.

609

610

Table 2. Distribution of Drug Classes by Number of Medications Used

	Number of Medications			
Drug Class	**0-5 (N=6943)**	**6-8 (N=6502)**	**9 or more (N=4756)**	**p-value**
A. Alimentary tract and metabolism	962 (13.9%)	3045 (46.8%)	4094 (86.1%)	<.0001
B. Blood and blood forming organs [excluding apixaban/warfarin]	2282 (32.9%)	4322 (66.5%)	4116 (86.5%)	<.0001
C. Cardiovascular system	6460 (93.0%)	6468 (99.5%)	4737 (99.6%)	<.0001
D. Dermatologicals	34 (0.5%)	96 (1.5%)	346 (7.3%)	<.0001
G. Genito-urinary system and sex hormones	173 (2.5%)	510 (7.8%)	936 (19.7%)	<.0001
H. Systemic hormonal preparations, excluding sex hormones and insulins	181 (2.6%)	508 (7.8%)	852 (17.9%)	<.0001
J. Antiinfectives for systemic use	44 (0.6%)	161 (2.5%)	347 (7.3%)	<.0001
L. Antineoplastic and immunomodulating agents	14 (0.2%)	60 (0.9%)	152 (3.2%)	<.0001
M. Musculo-skeletal system	202 (2.9%)	688 (10.6%)	1350 (28.4%)	<.0001
N. Nervous system	523 (7.5%)	1448 (22.3%)	2376 (50.0%)	<.0001
P. Antiparasitic products, insecticides and repellents	0 (0.0%)	13 (0.2%)	46 (1.0%)	<.0001
R. Respiratory system	164 (2.4%)	600 (9.2%)	1336 (28.1%)	<.0001
S. Sensory organs	41 (0.6%)	115 (1.8%)	300 (6.3%)	<.0001
V. Various	126 (1.8%)	247 (3.8%)	630 (13.2%)	<.0001
Interacting drugs				
≥1 combined P-gp and weak-moderate-strong CYP3A4 inhibitor	1128 (16.2%)	1431 (22.0%)	1301 (27.4%)	<.0001
≥1 combined P-gpGP and weak-moderate-strong CYP3A4 inducer	12 (0.2%)	34 (0.5%)	47 (1.0%)	<.0001
≥1 highly probable VKA inhibiting drug	8 (0.1%)	19 (0.3%)	33 (0.7%)	<.0001
≥1 highly probable VKA potentiating drug	973 (14.0%)	1406 (21.6%)	1387 (29.2%)	<.0001
Use of ASA,NSAIDs and/or Prednisone	956 (13.8%)	2064 (31.7%)	2362 (49.7%)	<.0001

Abbreviations: n = number of patients, P-gp = P-glycoprotein, CYP = Cytochrome P450, VKA = vitamin K antagonist, ASA = acetylsalicylic acid, NSAID = non-steroidal anti-inflammatory drug.

611

Table 3. Efficacy and Safety Outcomes by Number of Medications Used

	0-5 Meds	6-8 Meds		9 or more Meds		
Event	**Rate (n)**	**Rate (n)**	**Adjusted Hazard Ratio* (95% CI)**	**Rate (n)**	**Adjusted Hazard Ratio* (95% CI)**	**p-value**
Efficacy Outcomes						
Stroke/SE	1.29 (166)	1.48 (176)	1.270 (1.022 to 1.577)	1.57 (135)	1.539 (1.190 to 1.991)	0.0038
Ischemic or uncertain type of stroke	0.82 (106)	1.11 (132)	1.475 (1.136 to 1.915)	1.15 (99)	1.738 (1.275 to 2.369)	0.0010
All cause death	3.01 (396)	3.80 (462)	1.409 (1.229 to 1.616)	4.70 (414)	2.031 (1.735 to 2.377)	<.0001
Safety Outcomes						
Major bleeding	1.91 (224)	2.46 (267)	1.243 (1.036 to 1.491)	3.88 (298)	1.721 (1.414 to 2.095)	<.0001
Intracranial	0.54 (64)	0.55 (61)	1.025 (0.722 to 1.456)	0.62 (49)	1.153 (0.795 to 1.673)	0.7
Gastrointestinal	0.47 (56)	0.71 (78)	1.498 (1.062 to 2.111)	1.15 (90)	2.429 (1.740 to 3.391)	<.0001
Clinically relevant non-major bleeding	2.09 (243)	2.47 (267)	1.183 (0.994 to 1.408)	3.30 (252)	1.574 (1.319 to 1.877)	<.0001
Any bleeding	17.41 (1742)	21.40 (1908)	1.167 (1.092 to 1.247)	29.63 (1766)	1.452 (1.348 to 1.565)	<.0001
Net Benefit Outcomes						
Stroke/SE/major bleeding/all cause death	5.24 (665)	6.59 (769)	1.320 (1.187 to 1.468)	8.92 (743)	1.838 (1.631 to 2.071)	<.0001
Other Outcomes						
Permanent study drug discontinuation	14.32 (1699)	14.99 (1655)	1.053 (0.982 to 1.129)	17.44 (1372)	1.218 (1.123 to 1.322)	<.0001
Time in Therapeutic Range <66%#	53.2 (1823)	50.2 (1564)	0.887 (0.805 to 0.977)	44.9 (1044)	0.716 (0.644 to 0.795)	< .0001

Hazard ratios and p-value adjusted by country (strata), gender and age (spline)

* Hazard ratio vs. 0-5 meds

Values reported are percentage (number of patients) and unadjusted odd ratios for patients randomized to warfarin.

Abbreviations: n = number of patients, CI = confidence interval, meds = medications, SE = systemic embolism.

Table 4: Major bleeding with apixaban or warfarin according to the use of interacting drugs

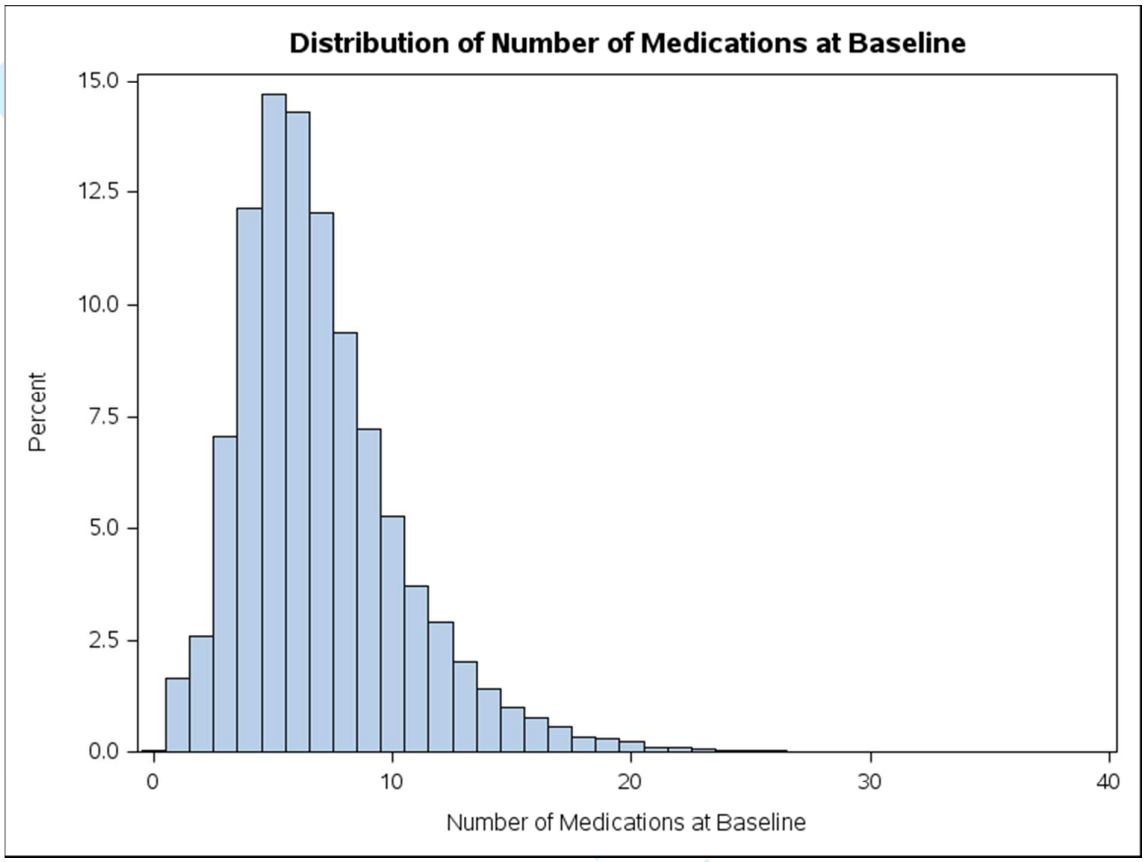
	Use of potentiating drug		No use of potentiating drug		
Interacting drugs	**Apixaban Rate (n)**	**Warfarin Rate (n)**	**Apixaban Rate (n)**	**Warfarin Rate (n)**	**P interaction**
≥ 1 combined P-gp and weak/moderate/strong CYP3A inhibitor	2.27 (72)	2.91 (93)	2.10 (255)	3.14 (369)	0.4
≥ 1 Highly probable VKA potentiating drug	2.03 (62)	3.16 (96)	2.16 (265)	3.07 (366)	0.6

Abbreviations: n = number of patients, PGP = P-glycoprotein, CYP = Cytochrome P450, VKA = vitamin K antagonist.

Figure 1.

Figure 2.

Supplementary Figure 1



Supplementary figure 1. Distribution of number of medications at baseline.

Supplementary Table 1. Baseline characteristics by number of baseline concomitant medications subcategorized by treatment allocation

	0-5 Meds		6-8 Meds		9 or More Meds	
Characteristic	**Apixaban (N=3424)**	**Warfarin (N=3519)**	**Apixaban (N=3320)**	**Warfarin (N=3182)**	**Apixaban (N=2376)**	**Warfarin (N=2380)**
Age, mean (SD), yrs	68, (10)	68, (10)	69, (9)	69, (10)	71, (9)	71, (9)
Male, no, (%)	2320 (67.8%)	2367 (67.3%)	2076 (62.5%)	2031 (63.8%)	1490 (62.7%)	1501 (63.1%)
Weight, mean (SD), kg	81, (19)	81, (18)	84, (21)	84, (21)	89, (23)	89, (23)
Body mass index, mean (SD), kg/m^2	28.2, (5.3)	28.3, (5.4)	29.4, (6.0)	29.6, (6.1)	30.7, (6.5)	30.8, (6.6)
Prior use of Vitamin K antagonists for >30 days, no (%)	1759 (51.4%)	1796 (51.0%)	1852 (55.8%)	1804 (56.7%)	1597 (67.2%)	1593 (66.9%)
Creatinine, mean (SD)	1.01, (0.24)	1.02, (0.25)	1.06, (0.28)	1.06, (0.28)	1.12, (0.32)	1.12, (0.32)
Region of enrollment, no. (%)						
North America	362 (10.6%)	374 (10.6%)	702 (21.1%)	651 (20.5%)	1185 (49.9%)	1200 (50.4%)
Latin America	905 (26.4%)	904 (25.7%)	670 (20.2%)	636 (20.0%)	168 (7.1%)	185 (7.8%)
Europe	1549 (45.2%)	1579 (44.9%)	1409 (42.4%)	1402 (44.1%)	714 (30.1%)	690 (29.0%)
Asia	608 (17.8%)	662 (18.8%)	539 (16.2%)	493 (15.5%)	309 (13.0%)	305 (12.8%)
HAS-BLED score, mean (SD)	1.46, (0.96)	1.45, (0.96)	1.78, (1.01)	1.76, (1.03)	2.23, (1.06)	2.27, (1.04)
$CHADS_2$ score, mean (SD)	1.87, (1.02)	1.88, (1.02)	2.15, (1.08)	2.14, (1.09)	2.41, (1.15)	2.46, (1.19)
$CHADS_2$ score, no (%)						
≤1	1533 (44.8%)	1560 (44.3%)	1037 (31.2%)	1020 (32.1%)	530 (22.3%)	503 (21.1%)
2	1139 (33.3%)	1170 (33.2%)	1217 (36.7%)	1183 (37.2%)	906 (38.1%)	901 (37.9%)
≥3	752 (22.0%)	789 (22.4%)	1066 (32.1%)	979 (30.8%)	940 (39.6%)	976 (41.0%)
Low dose apixaban/placebo (2.5 mg bid) received	122 (3.6%)	131 (3.7%)	166 (5.0%)*	122 (3.8%)*	140 (5.9%)	150 (6.3%)
Comorbidities organized by organ system, no. (%)						
Cardiovascular						
CAD	897 (26.2%)	898 (25.6%)	1118 (33.7%)	1066 (33.6%)	1032 (43.5%)	1031 (43.3%)
Prior MI	295 (8.6%)	269 (7.7%)	501 (15.1%)	484 (15.2%)	523 (22.0%)	513 (21.6%)
History of PCI/CABG	192 (5.6%)	177 (5.0%)	430 (13.0%)	385 (12.1%)	653 (27.5%)	639 (26.8%)
Congestive Heart Failure within 3 Months	958 (28.0%)	973 (27.6%)	1127 (33.9%)	1067 (33.5%)	699 (29.4%)	717 (30.1%)
At Least Moderate Valvular Heart Disease	458 (13.4%)	468 (13.3%)	611 (18.4%)	581 (18.3%)	560 (23.6%)	556 (23.4%)
Syncope in Last 5 years	136 (4.0%)	122 (3.5%)	147 (4.4%)	132 (4.2%)	153 (6.4%)	169 (7.1%)
Hypertension with Pharmacological Treatment	2893 (84.5%)	2951 (83.9%)	2941 (88.6%)	2821 (88.7%)	2128 (89.6%)*	2182 (91.7%)*
PAD	88 (2.6%)	105 (3.0%)	150 (4.6%)	140 (4.4%)	204 (8.7%)	197 (8.4%)
Aortic Aneurysm	26 (0.8%)	20 (0.6%)	50 (1.5%)	34 (1.1%)	65 (2.8%)	74 (3.1%)
Neurological/Cerebrovascular						
Carotid Stenosis	29 (0.8%)	25 (0.7%)	48 (1.4%)	45 (1.4%)	103 (4.3%)	87 (3.7%)
TIA	138 (4.0%)	164 (4.7%)	164 (4.9%)	151 (4.7%)	158 (6.7%)	179 (7.5%)
Stroke	383 (11.2%)	425 (12.1%)	385 (11.6%)	365 (11.5%)	277 (11.7%)	292 (12.3%)
Dementia	10 (0.3%)	12 (0.4%)	18 (0.6%)	11 (0.4%)	21 (0.9%)	24 (1.1%)
Epilepsy	10 (0.3%)	12 (0.4%)	22 (0.7%)	27 (0.9%)	21 (0.9%)	20 (0.9%)

Supplementary Table 1. Baseline characteristics by number of baseline concomitant medications subcategorized by treatment allocation

	0-5 Meds		6-8 Meds		9 or More Meds	
Characteristic	**Apixaban (N=3424)**	**Warfarin (N=3519)**	**Apixaban (N=3320)**	**Warfarin (N=3182)**	**Apixaban (N=2376)**	**Warfarin (N=2380)**
Pulmonary						
COPD	211 (6.2%)	224 (6.4%)	317 (9.6%)	309 (9.8%)	442 (18.6%)	447 (18.8%)
Asthma	77 (2.3%)	80 (2.3%)	122 (3.7%)	128 (4.0%)	211 (8.9%)	251 (10.6%)
Sleep Apnea	72 (2.1%)	73 (2.1%)	138 (4.2%)	124 (3.9%)	310 (13.1%)	296 (12.5%)
Gastrointestinal						
Dyspepsia	193 (5.6%)	181 (5.2%)	229 (6.9%)	216 (6.8%)	272 (11.5%)	284 (11.9%)
GE Reflux Disease	164 (4.8%)	151 (4.3%)	253 (7.7%)	274 (8.6%)	540 (22.8%)	534 (22.5%)
Peptic Ulcer Disease	193 (5.6%)	190 (5.4%)	211 (6.4%)	206 (6.5%)	210 (8.8%)	196 (8.2%)
GI Surgery	246 (7.2%)	263 (7.5%)	316 (9.5%)	290 (9.1%)	298 (12.5%)	277 (11.7%)
Chronic Liver Disease	94 (2.7%)	96 (2.7%)	106 (3.2%)	87 (2.7%)	65 (2.7%)	56 (2.4%)
Endocrine						
Hypo/Hyperthyrodism	210 (6.2%)	219 (6.2%)	389 (11.7%)	344 (10.8%)	450 (19.0%)	428 (18.0%)
Diabetes	403 (11.8%)	403 (11.5%)	827 (24.9%)	776 (24.4%)	1054 (44.4%)	1084 (45.5%)
End organ Damage due to DM	32 (0.9%)	43 (1.2%)	108 (3.3%)	111 (3.5%)	229 (9.7%)	230 (9.7%)
Musculoskeletal						
Falls within 1 year	81 (2.7%)*	59 (1.9%)*	96 (3.2%)	119 (4.1%)	209 (9.3%)	189 (8.4%)
Previous Non-Traumatic Fracture	147 (4.3%)	152 (4.3%)	171 (5.2%)	168 (5.3%)	229 (9.7%)	207 (8.7%)
Osteoporosis	75 (2.2%)	76 (2.2%)	146 (4.4%)	152 (4.8%)	266 (11.2%)	255 (10.7%)
Renal						
Chronic Kidney Disease	218 (6.4%)	216 (6.1%)	260 (7.8%)	260 (8.2%)	270 (11.4%)	283 (11.9%)
Creatine Clearance < 50 mL/min	444 (13.0%)	483 (13.8%)	573 (17.3%)	539 (17.0%)	479 (20.2%)	491 (20.7%)
Hematological						
History of Anemia	97 (2.8%)	113 (3.2%)	199 (6.0%)	160 (5.0%)	354 (14.9%)	322 (13.5%)
Thrombocytopenia (platelet at baseline < 150)	261 (7.8%)	249 (7.3%)	245 (7.6%)	222 (7.1%)	177 (7.7%)	155 (6.7%)
Bleeding History	392 (11.4%)	387 (11.0%)	543 (16.4%)	486 (15.3%)	590 (24.8%)	642 (27.0%)
Number of organ systems affected (median, 25th-75th)	2, 1-3	2, 1-3	2, 2-3	2, 2-3	3, 2-4	3, 3-4

*P-value<0.05 between apixaban and warfarin allocation;
Abbreviations: n = number of patients, sd = standard deviation, yrs = years, no = number, kg = kilogram, m = meter, CAD = coronary artery disease, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, PAD = peripheral artery disease, TIA = transient ischemic attack, COPD = chronic obstructive pulmonary disease, GE = gastroesophageal reflux disease, GI = gastrointestinal, DM = diabetes mellitus, mL = milliliter, min = minute.

Supplementary Table 2A. Distribution of Drug Classes by Number of Medications Used – U.S. Patients

		Number of Medications			
Drug Class	**All (N=3417)**	**0-5 (N=467)**	**6-8 (N=970)**	**9 or more (N=1980)**	**p-value**
A. Alimentary tract and metabolism	2508 (73%)	100 (21.4%)	603 (62.2%)	1805 (91.2%)	<.0001
B. Blood and blood forming organs [excluding apixaban/warfarin]	2722 (80%)	209 (44.8%)	720 (74.2%)	1793 (90.6%)	<.0001
C. Cardiovascular system	3323 (97%)	400 (85.7%)	956 (98.6%)	1967 (99.3%)	<.0001
D. Dermatologicals	270 (8%)	8 (1.7%)	44 (4.5%)	218 (11.0%)	<.0001
G. Genito-urinary system and sex hormones	717 (21%)	29 (6.2%)	146 (15.1%)	542 (27.4%)	<.0001
H. Systemic hormonal preparations, excluding sex hormones and insulins	528 (15%)	19 (4.1%)	87 (9.0%)	422 (21.3%)	<.0001
J. Antiinfectives for systemic use	214 (6%)	3 (0.6%)	36 (3.7%)	175 (8.8%)	<.0001
L. Antineoplastic and immunomodulating agents	95 (3%)	4 (0.9%)	18 (1.9%)	73 (3.7%)	0.0004
M. Musculo-skeletal system	824 (24%)	18 (3.9%)	154 (15.9%)	652 (32.9%)	<.0001
N. Nervous system	1529 (45%)	63 (13.5%)	340 (35.1%)	1126 (56.9%)	<.0001
P. Antiparasitic products, insecticides and repellents	20 (0.6%)	0 (0.0%)	1 (0.1%)	19 (1.0%)	0.0034
R. Respiratory system	850 (25%)	19 (4.1%)	145 (14.9%)	686 (34.6%)	<.0001
S. Sensory organs	207 (6%)	4 (0.9%)	34 (3.5%)	169 (8.5%)	<.0001
V. Various	400 (12%)	10 (2.1%)	52 (5.4%)	338 (17.1%)	<.0001
Interacting drugs					
≥1 combined PGP and weak-moderate-strong CYP3A4 inhibitor	913 (26.7%)	87 (18.6%)	244 (25.2%)	582 (29.4%)	<.0001
≥1 combined PGP and weak-moderate-strong CYP3A4 inducer	12 (0.4%)	1 (0.2%)	4 (0.4%)	7 (0.4%)	0.9
≥1 highly probable VKA inhibiting drug	24 (0.7%)	1 (0.2%)	6 (0.6%)	17 (0.9%)	0.3
≥1 highly probable VKA potentiating drug	772 (22.6%)	45 (9.6%)	167 (17.2%)	560 (28.3%)	<.0001
Use of ASA,NSAIDs and/or Prednisone	1555 (45.5%)	91 (19.5%)	371 (38.2%)	1093 (55.2%)	<.0001

Abbreviations: n = number of patients, PGP = P-Glycoprotein, CYP = Cytochrome P450, VKA = vitamin K antagonist, ASA = acetylsalicylic acid, NSAID = non-steroidal anti-inflammatory drug.

Supplementary table 2B. Distribution of Drug Classes by Number of Medications Used - non-U.S. Patients

		Number of Medications			
Drug Class	**All (N=14784)**	**0-5 (N=6476)**	**6-8 (N=5532)**	**9 or more (N=2776)**	**p-value**
A. Alimentary tract and metabolism	5593 (38%)	862 (13.3%)	2442 (44.1%)	2289 (82.5%)	<.0001
B. Blood and blood forming organs [excluding apixaban/warfarin]	7998 (54%)	2073 (32.0%)	3602 (65.1%)	2323 (83.7%)	<.0001
C. Cardiovascular system	14342 (97%)	6060 (93.6%)	5512 (99.6%)	2770 (99.8%)	<.0001
D. Dermatologicals	206 (1.4%)	26 (0.4%)	52 (0.9%)	128 (4.6%)	<.0001
G. Genito-urinary system and sex hormones	902 (6%)	144 (2.2%)	364 (6.6%)	394 (14.2%)	<.0001
H. Systemic hormonal preparations, excluding sex hormones and insulins	1013 (7%)	162 (2.5%)	421 (7.6%)	430 (15.5%)	<.0001
J. Antiinfectives for systemic use	338 (2%)	41 (0.6%)	125 (2.3%)	172 (6.2%)	<.0001
L. Antineoplastic and immunomodulating agents	131 (0.9%)	10 (0.2%)	42 (0.8%)	79 (2.8%)	<.0001
M. Musculo-skeletal system	1416 (10%)	184 (2.8%)	534 (9.7%)	698 (25.1%)	<.0001
N. Nervous system	2818 (19%)	460 (7.1%)	1108 (20.0%)	1250 (45.0%)	<.0001
P. Antiparasitic products, insecticides and repellents	39 (0.3%)	0 (0.0%)	12 (0.2%)	27 (1.0%)	<.0001
R. Respiratory system	1250 (8%)	145 (2.2%)	455 (8.2%)	650 (23.4%)	<.0001
S. Sensory organs	249 (1.7%)	37 (0.6%)	81 (1.5%)	131 (4.7%)	<.0001
V. Various	603 (4%)	116 (1.8%)	195 (3.5%)	292 (10.5%)	<.0001
Interacting drugs					
≥1 combined PGP and weak-moderate-strong CYP3A4 inhibitor	2947 (19.9%)	1041 (16.1%)	1187 (21.5%)	719 (25.9%)	<.0001
≥1 combined PGP and weak-moderate-strong CYP3A4 inducer	81 (0.5%)	11 (0.2%)	30 (0.5%)	40 (1.4%)	<.0001
≥1 highly probable VKA inhibiting drug	36 (0.2%)	7 (0.1%)	13 (0.2%)	16 (0.6%)	0.0002
≥1 highly probable VKA potentiating drug	2994 (20.3%)	928 (14.3%)	1239 (22.4%)	827 (29.8%)	<.0001
Use of ASA,NSAIDs and/or Prednisone	3827 (25.9%)	865 (13.4%)	1693 (30.6%)	1269 (45.7%)	<.0001

Abbreviations: n = number of patients, PGP = P-Glycoprotein, CYP = Cytochrome P450, VKA = vitamin K antagonist, ASA = acetylsalicylic acid, NSAID = non-steroidal anti-inflammatory drug.