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

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Abstract

Objective: Polypharmacy is associated with frailty and adverse clinical events. Compared with warfarin, apixaban is more effective in preventing stroke and safer in patients with atrial fibrillation (AF). However, it has not been shown if these benefits are consistent in patients treated with many concomitant medications.

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

Results: The median number of concomitant medications was 6 (interquartile range 5–9). When comparing tertiles, patients using more medications were older, more often female, and were more often from North America. Comorbidities were more frequently present in patients using more medications. During a median follow-up of 1.8 years, the rates of thromboembolic and bleeding outcomes increased across tertiles. The superiority of apixaban when compared with warfarin in reducing stroke and systemic embolism was consistent regardless of the number of concomitant medications (interaction p-value=0.82). In terms of reducing major bleeding, the magnitude of benefit with apixaban decreased with the number of medications taken (interaction p-value=0.017).

Conclusions: In ARISTOTLE, both ischemic and hemorrhagic complications occurred more frequently in patients treated with a greater number of concomitant medications. The benefits of apixaban in reducing stroke were maintained, regardless of the number of medications taken. In terms of safety and net clinical benefit, while the rates were consistently lower with apixaban, the magnitude of benefit with apixaban decreased with the number of concomitant medications. Thus, apixaban is more effective than warfarin and at least as safe in patients with AF and polypharmacy.

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, and undertreatment has been associated with adverse outcome.[2] This also holds true for those patients at high risk of ischemic events and is always challenging in patients with various comorbidities who require many concomitant medications.[3,4] On average, patients with AF use about six different medications.[5,6] Given that polypharmacy is generally defined as the use of five or more concomitant medications, this is very common in patients with AF.[7] In a variety of populations, polypharmacy has been associated with multiple comorbidities and frailty.[8-12] In addition, it has been related to a higher risk of death and bleeding complications, including in patients with AF.[5,9-19]

With the introduction of apixaban, a safer alternative to warfarin has become available which also proved its value in patients considered unsuitable for warfarin.[20,21] Especially in this group of patients with more comorbidity and various concomitant medications, it is interesting to compare the efficacy and safety of apixaban with warfarin. Thus, we performed a post-hoc analysis of the ARISTOTLE trial (Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation).[21] In this post-hoc analysis, we addressed the occurrence of clinical events in anticoagulated patients with AF and 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.[21,22] 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

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 cytochrome (CYP) 3A4 (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.

We assessed outcomes in relation to the number of concomitant medications used at the time of randomization. The study drug (apixaban or warfarin) and the matching placebo were counted as

one drug. Polypharmacy was defined as the use of five or more concomitant drugs. All medications were categorized according to the Anatomical Therapeutic Chemical classification system.[23]

Clinical outcomes

The median follow-up duration in ARISTOTLE was 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), all-cause death, and myocardial infarction. Myocardial infarction was defined as symptoms with an elevation of biomarker values (troponin, creatinine kinase, or creatinine kinase myocardial band) of at least twice the upper limit of normal, or the presence of new significant Q-waves in ≥2 contiguous ECG leads.

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.[24] 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 stroke, systemic embolism, and major bleeding. We also studied this combination with the addition of all-cause death. Finally, we studied premature permanent study drug discontinuation and the time in therapeutic range (TTR) according to the Rosendaal method.[25]

Statistical analysis

Patients were classified in three groups based on the tertiles of distribution of the number of concomitant medications received at baseline. Baseline characteristics, comorbidities organized by organ system, and drug classes were summarized for the three groups with mean and standard deviation 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 stratified by country. 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.[26] Final study results of the ARISTOTLE trial were disseminated to study participants through their treating physicians.

Results

Baseline characteristics

Data of the medication use at baseline were available for all 18,201 patients enrolled in ARISTOTLE. The median number of medications used was 6 (5, 9) and polypharmacy was present in 13,932

(76.5%) patients (Figure 1). Patients using more medications were older, more often female, and less often warfarin-naïve at study entry (Table 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. Overall, however, comorbidities present at baseline were strongly associated with the number of medications used. Exceptions were a history of stroke, liver disease, and thrombocytopenia. The $CHADS_2$ and HAS-BLED scores increased across tertiles of increasing number of concomitant medications. As expected, the randomized treatment was well balanced across tertiles.

Drug classification according to organ or system

All medications were categorized according to the Anatomical Therapeutic Chemical classification system. Between tertiles, the median number of organs or systems affected by concomitant medications increased from 2 (2, 3) for patients using 0–5 medications to 5 (4, 5) for patients using 9 or more medications (Table 2).

Apart from the study medication (apixaban or warfarin), medications affecting the cardiovascular system were the most common (97.1%), followed by those influencing the blood and blood forming organs (58.9%), and the alimentary tract and metabolism (44.5%) (Table 2). The percentage of patients using one or more medications affecting these systems significantly increased across tertiles, which was true also for all other categories. For all drug categories, the percentage of patients using at least one medication was higher in the U.S. when compared with patients from the rest of the world (Supplementary Table 1a and 1b).

Clinical outcomes according to the number of concomitant medications

Event rates with associated hazard ratios (HR) adjusted for age, sex, and country are depicted in Table 3.

Stroke and systemic embolism

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 ($p<0.001$). When categorizing the type of stroke, the effect observed for the primary efficacy endpoint was consistent for strokes of ischemic or undetermined origin. The secondary efficacy outcomes also proved strongly associated with the number of concomitant medications, with a 2–3-fold increased risk for both myocardial infarction and all-cause death, when the highest tertile (≥9 medications) was compared with the lowest (0–5 medications) ($p<0.001$).

Bleeding

The risk of major bleeding for the group of 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 1.041.49; 9 or more drugs: adjusted HR 1.72, 95% CI 1.41–2.10). When subdividing the major bleeding according to the location, no significant difference between tertiles was observed for intracranial bleeding ($p=0.73$), while the event rate for gastrointestinal bleeding significantly increased across tertiles. For the combination of major and clinically relevant non-major bleeding events, the event rate increased from 3.92 in patients using 0–5 medications to 7.03 per 100 patient-years at risk for those using 9 or more medications ($p<0.001$).

Net thrombotic and bleeding 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 up to 1.84 (95% CI 1.631–2.071) for patients using 9 or more medications when compared with those using 0–5.

Other outcomes

With increasing numbers of medications, the risk of permanently discontinuing the study drug 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). The proportion of patients assigned to warfarin with a 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, 5–8, and 9 or more respectively, p<0.001) (Table 3). As for the concomitant use of aspirin, proportions were 12.4%, 27.3%, and 38.2%, respectively (p<0.001) (Table 2).

Treatment effect

Table 4 outlines 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, treatment with apixaban was superior to warfarin irrespective of the number of medications used (p interaction=0.82). Also for the secondary efficacy outcomes, no significant interactions were observed.

With regard to the benefit in reducing major bleeding, relative risk reductions for apixaban decreased with increasing number of drugs (p interaction=0.017), corresponding with absolute reductions in major bleeding rate for apixaban when compared with warfarin from 1.28 to 0.82 to 0.66 per 100 patient-years in patients using 0–5, 6–8, and 9 or more medications, respectively. For gastrointestinal major bleeding, similar observations were made (HR 0.60, 0.81, 1.14 for 0–5, 6–8, and ≥9 medications, respectively). Regarding intracranial bleeding, the benefit of apixaban remained consistent across tertiles. Also for the secondary safety outcome of major or clinically relevant non-major bleeding, event rates were lower for patient using apixaban when compared with warfarin, but the relative benefit decreased when more concomitant medications were used (p interaction 0.048). For the outcome of any bleeding, no significant interaction was present.

With regard to the combined outcome of stroke, systemic embolism, major bleeding and all-cause death, the point estimate was in favor of apixaban consistently throughout polypharmacy groups (p interaction=0.10)

Discussion

In this post-hoc analysis of the ARISTOTLE trial, we demonstrated that polypharmacy is common among patients with AF and that the number of concomitant medications is associated with increased comorbidity. Being enrolled in the United States was strongly associated with use of a greater number of medications. 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 associated with the presence of various comorbidities resulting in the prescription of numerous medications.[27] In general, patients with AF use about 4 to 6 different medications and polypharmacy (≥5 concomitant medications) is present in about 40–60%.[12,19] Interestingly, previous studies demonstrated a relation between the number of concomitant medications and adverse clinical outcomes, both in AF and non-AF populations.[5,9-19] In addition, studies focusing on elderly populations have linked polypharmacy to adverse drug reactions, falls, disability, and frailty.[9-11]
In our study population of patients with AF participating in the ARISTOTLE trial, polypharmacy is also very common with over 75% of the population using 5 or more medications and about 20% using at least 10 concomitant medications. Moreover, similar to previous studies, we reported a higher risk for adverse clinical outcomes during follow-up in patients using more medications. Of interest, this was observed for ischemic and bleeding endpoints as well as for all-cause mortality.

Notably, this higher risk of adverse outcomes should be placed in the context of the strong 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 an easily obtainable marker that relates to comorbidity/frailty. As such, we performed adjustments only for age, sex, and country of randomization. The latter is of special importance given the differences in prescription patterns between countries. This is not only related to a higher burden of comorbidity in patients in the U.S. In fact, there was also a lower threshold to treat with multiple medications even with limited concomitant disease (exploratory analyses, data not shown).

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.[21]

Overall, the use of apixaban was associated with a 31% risk reduction in major bleeding.[21] 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 diminishes 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 clear benefit for apixaban (0–5 medications) to no apparent difference (≥9 medications) between both oral anticoagulants.

In the ROCKET AF trial, which compared rivaroxaban versus warfarin, it was observed that the risk for major bleeding in patients using fewer medications (0–4) was lower (adjusted HR 0.69, 95% CI 0.51–0.94) than observed in the entire study population (HR 1.04, 95% CI 0.90–1.20).[19] No data on mortality were reported in this post-hoc analysis of ROCKET AF. 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.[21]

In ARISTOTLE as well as in ROCKET AF, patients with polypharmacy were older.[19,21] 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.[28,29] This implies that our findings cannot be inferred to the 'elderly patient' in general. In fact, our findings refer to the group of patients with multiple comorbidities and medications, irrespective of age and sex. A possible explanation for the attenuation of the observed safety benefit of apixaban in the patients with many concomitant medications relates to the observed differences in the baseline risk profile. We demonstrated that various risk factors for gastrointestinal bleeding complications (e.g., previous gastric ulcer, gastrointestinal surgery, dyspepsia, aspirin use) were more prevalent among patients with polypharmacy. In addition, other non-gastrointestinal risk factors for bleeding were also more often present in patients with more concomitant medications (e.g., older age, renal impairment, anemia, diabetes, and previous bleeding).[30] Possibly, while apixaban is a safer drug in a general population with AF, the risk difference in bleeding may be lower in patients of the highest tertile due to the better INR control in this subgroup of patients.[31,32]

The 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.[16] 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.[16] However, these patients are much younger and less fragile when compared with a patients with AF. Interestingly, in an analysis of 'fragile' patients with symptomatic venous thromboembolism, rivaroxaban proved safer than warfarin.[33] 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.[34] In this context, polypharmacy could be used as a surrogate for multi-morbidity/frailty. Future research may focus on incorporation of the key frailty criteria, for example

the Fried criteria, which may help to identify a group of potentially higher-risk patients that is often underrepresented in clinical trials.[35] 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.[36]

Limitations

There are several limitations of this study. First, it is a retrospective and post-hoc analysis. Second, we only assessed drug use at baseline and did not take into account drug changes during follow-up. Third, we have no information about the reason or appropriateness for drug prescription or omissions. Fourth, given the lack of a uniform definition of polypharmacy, we used a cut-off value of 5 or more drugs. Due to the high occurrence of polypharmacy and our aim to study the effect of the number of drugs on adverse clinical outcomes, we categorized patients into tertiles according to the number of medications used and decided not just to compare patients with or without polypharmacy. With regard to generalizability, our findings may not apply to an unselected population with AF, given the various inclusion and exclusion criteria of the trial that were applied.

Conclusions

In patients using oral anticoagulation in the setting of AF, polypharmacy is common and the use of more concomitant medications was associated with a higher risk of adverse clinical outcomes. More baseline medications were used in the United States than the rest of the geographic regions. Apixaban was superior to warfarin in terms of efficacy, regardless of the number of medications taken. The magnitude of benefit with apixaban on less major bleeding decreased with the number of concomitant medications, although the bleeding rates with apixaban were consistently lower with apixaban. Thus, apixaban is more effective than and at least as safe as warfarin in patients with AF, regardless of polypharmacy.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

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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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.

Data Sharing

No additional data available.

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Figure Legends

Figure 1. Distribution of number of medications at baseline.

Table 1. Baseline Characteristics

	Number of Medications			
Characteristic	**0-5 (N=6943)**	**6-8 (N=6502)**	**9 or more (N=4756)**	**p-value**
Age, mean (SD), yrsa	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 enrolment, 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. (%)				0.1256
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%)	0.7729
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

	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
Pep 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%)	0.3882
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%)	0.7651
Bleeding History	779 (11.2%)	1029 (15.8%)	1232 (25.9%)	<.0001

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	6927 (99.8%)	6499 (100.0%)	4755 (100.0%)	0.0005
B. Blood and blood forming organs [excluding apixaban/warfarin]	2282 (32.9%)	4322 (66.5%)	4116 (86.5%)	<.0001
B. Aspirin	856 (12.4%)	1768 (27.3%)	1810 (38.2%)	<.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

Table 3. Association Between Number of Concomitant Medications and Endpoints – Adjusted analyses

	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**
Net Benefit Endpoints						.
Stroke/SE/major bleeding	2.79 (353)	3.54 (413)	1.264 (1.093 - 1.462)	5.06 (421)	1.686 (1.435 - 1.979)	<.0001
Stroke/SE/major bleeding/all cause death	5.24 (665)	6.59 (769)	1.320 (1.187 - 1.468)	8.92 (743)	1.838 (1.631 - 2.071)	<.0001
Safety Endpoints						
Major bleeding	1.91 (224)	2.46 (267)	1.243 (1.036 - 1.491)	3.88 (298)	1.721 (1.414 - 2.095)	<.0001
Intracranial	0.54 (64)	0.55 (61)	1.025 (0.722 - 1.456)	0.62 (49)	1.153 (0.795 - 1.673)	0.7339
Gastrointestinal	0.47 (56)	0.71 (78)	1.498 (1.062 - 2.111)	1.15 (90)	2.429 (1.740 - 3.391)	<.0001
Major or clinically relevant non-major bleeding	3.92 (452)	4.81 (513)	1.179 (1.036 - 1.342)	7.03 (525)	1.529 (1.326 - 1.764)	<.0001
Any bleeding	17.41 (1742)	21.40 (1908)	1.167 (1.092 - 1.247)	29.63 (1766)	1.452 (1.348 - 1.565)	<.0001
Efficacy Endpoints						
Stroke/SE	1.29 (166)	1.48 (176)	1.270 (1.022 - 1.577)	1.57 (135)	1.539 (1.190 - 1.991)	0.0038
Ischemic or uncertain type of stroke	0.82 (106)	1.11 (132)	1.475 (1.136 - 1.915)	1.15 (99)	1.738 (1.275 - 2.369)	0.0010
Myocardial infarction	0.34 (44)	0.49 (58)	1.383 (0.925 - 2.068)	1.04 (90)	2.435 (1.613 - 3.675)	<.0001
All cause death	3.01 (396)	3.80 (462)	1.409 (1.229 - 1.616)	4.70 (414)	2.031 (1.735 - 2.377)	<.0001
Stroke/SE/all cause death	3.91 (503)	4.84 (575)	1.368 (1.210 - 1.546)	5.94 (511)	1.906 (1.656 - 2.193)	<.0001
Permanent Study Drug Discontinuation	14.32 (1699)	14.99 (1655)	1.053 (0.982 - 1.129)	17.44 (1372)	1.218 (1.123 - 1.322)	<.0001
Time in Therapeutic Range <66%[#]	53.2 (1823)	50.2 (1564)	0.887 (0.805 – 0.977)	44.9 (1044)	0.716 (0.644 – 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 odds ratios for patients randomized to warfarin.

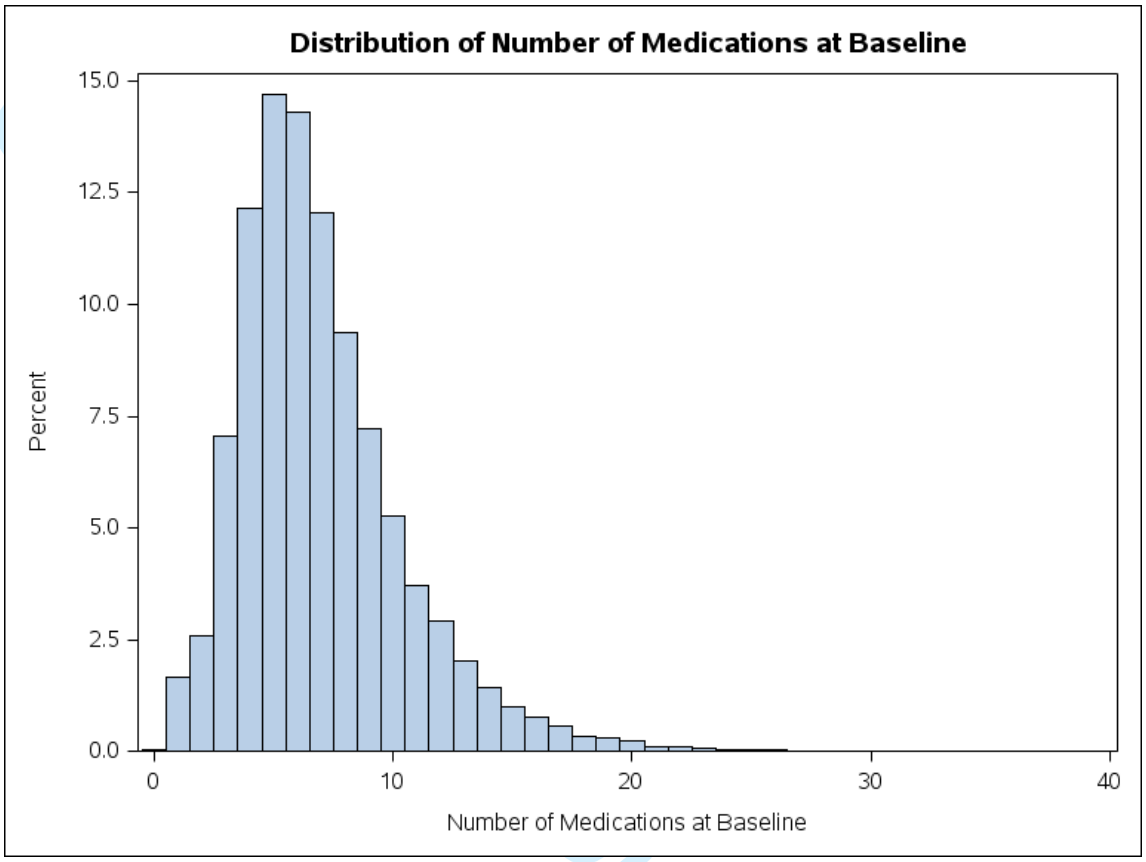
Table 4. Association Between Randomized Treatments and Endpoints by Number of Concomitant Medications

	Rate (n)		Hazard Ratio (95% CI)	Interaction
Event	**Apixaban**	**Warfarin**	**Apixaban vs. Warfarin**	**p-value**
Net Benefit Endpoints				
Stroke/SE/major bleeding				0.0659
0-5 meds	2.15 (136)	3.42 (217)	0.630 (0.509 - 0.781)	
6-8 meds	3.15 (188)	3.95 (225)	0.799 (0.658 - 0.969)	
9 or more meds	4.74 (197)	5.38 (224)	0.883 (0.729 - 1.069)	
Stroke/SE/major bleeding/all cause death				0.1018
0-5 meds	4.52 (286)	5.97 (379)	0.758 (0.650 - 0.883)	
6-8 meds	6.05 (361)	7.15 (408)	0.845 (0.734 - 0.974)	
9 or more meds	8.70 (362)	9.14 (381)	0.953 (0.826 - 1.101)	
Safety Endpoints				
Major bleeding				0.0173
0-5 meds	1.27 (75)	2.55 (149)	0.502 (0.381 - 0.663)	
6-8 meds	2.06 (115)	2.88 (152)	0.715 (0.561 - 0.911)	
9 or more meds	3.55 (137)	4.21 (161)	0.844 (0.672 - 1.060)	
Major bleeding: Intracranial				0.3685
0-5 meds	0.37 (22)	0.71 (42)	0.527 (0.314 - 0.882)	
6-8 meds	0.34 (19)	0.79 (42)	0.428 (0.249 - 0.736)	
9 or more meds	0.28 (11)	0.97 (38)	0.287 (0.147 - 0.561)	
Major bleeding: Gastrointestinal				0.1759
0-5 meds	0.36 (21)	0.59 (35)	0.601 (0.350 - 1.033)	
6-8 meds	0.64 (36)	0.79 (42)	0.809 (0.518 - 1.262)	
9 or more meds	1.23 (48)	1.08 (42)	1.135 (0.750 - 1.717)	
Major or clinically relevant non-major bleeding				0.0475
0-5 meds	2.88 (167)	4.97 (285)	0.583 (0.481 - 0.705)	
6-8 meds	3.83 (211)	5.86 (302)	0.655 (0.549 - 0.780)	
9 or more meds	6.25 (235)	7.82 (290)	0.800 (0.673 - 0.950)	
Any bleeding				0.8321
0-5 meds	14.54 (747)	20.45 (995)	0.723 (0.657 - 0.795)	
6-8 meds	17.57 (835)	25.77 (1073)	0.696 (0.636 - 0.762)	
9 or more meds	24.64 (774)	35.19 (992)	0.718 (0.654 - 0.789)	
Efficacy Endpoints				
Stroke/SE				0.8203
0-5 meds	1.19 (76)	1.39 (90)	0.859 (0.633 - 1.165)	
6-8 meds	1.29 (78)	1.69 (98)	0.761 (0.566 - 1.025)	
9 or more meds	1.35 (58)	1.79 (77)	0.759 (0.539 - 1.067)	
Ischemic or uncertain type of stroke				0.8145
0-5 meds	0.83 (53)	0.82 (53)	1.017 (0.695 - 1.488)	
6-8 meds	1.04 (63)	1.19 (69)	0.874 (0.621 - 1.230)	
9 or more meds	1.07 (46)	1.23 (53)	0.877 (0.591 - 1.303)	
Myocardial infarction				0.9519

Table 4. Association Between Randomized Treatments and Endpoints by Number of Concomitant Medications

	Rate (n)		Hazard Ratio (95% CI)	Interaction
Event	**Apixaban**	**Warfarin**	**Apixaban vs. Warfarin**	**p-value**
0-5 meds	0.33 (21)	0.35 (23)	0.933 (0.516 - 1.685)	
6-8 meds	0.46 (28)	0.51 (30)	0.897 (0.536 - 1.502)	
9 or more meds	0.95 (41)	1.14 (49)	0.837 (0.553 - 1.267)	
All cause death				0.8124
0-5 meds	2.78 (181)	3.24 (215)	0.858 (0.704 - 1.046)	
6-8 meds	3.57 (222)	4.04 (240)	0.886 (0.738 - 1.063)	
9 or more meds	4.55 (200)	4.85 (214)	0.939 (0.774 - 1.138)	
Stroke/SE/all cause death				0.8771
0-5 meds	3.65 (233)	4.16 (270)	0.876 (0.735 - 1.044)	
6-8 meds	4.51 (274)	5.18 (301)	0.871 (0.740 - 1.026)	
9 or more meds	5.70 (245)	6.18 (266)	0.924 (0.777 - 1.099)	
Other Endpoints				
Permanent Study Drug Discontinuation				0.3624
0-5 meds	13.47 (798)	15.17 (901)	0.892 (0.811 - 0.981)	
6-8 meds	14.00 (796)	16.04 (859)	0.877 (0.796 - 0.965)	
9 or more meds	17.13 (677)	17.75 (695)	0.966 (0.869 - 1.074)	

Figure 1



Supplementary Tables

Supplementary Table 1A. Distribution of Drug Classes by Number of Medications Used - US 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	3415 (99.9%)	466 (99.8%)	969 (99.9%)	1980 (100.0%)	0.0963
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

Supplementary table 1B. Distribution of Drug Classes by Number of Medications Used - non-US 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	14766 (99.9%)	6461 (99.8%)	5530 (100.0%)	2775 (100.0%)	0.0033
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