Outcomes of apixaban versus warfarin in patients with atrial fibrillation and multi-morbidity: Insights from the ARISTOTLE trial

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Background Patients with atrial fibrillation (AF) often have multi-morbidity, defined as ≥3 comorbid conditions. Multi-morbidity is associated with polypharmacy, adverse events, and frailty potentially altering response to anticoagulation. We sought to describe the prevalence of multi-morbidity among older patients with AF and determine the association between multi-morbidity, clinical outcomes, and the efficacy and safety of apixaban compared with warfarin.

Methods In this post-hoc subgroup analysis of the ARISTOTLE trial, we studied enrolled patients age ≥ 55 years (n = 16,800). Patients were categorized by the number of comorbid conditions at baseline: no multi-morbidity (0–2 comorbid conditions), moderate multi-morbidity (3–5 comorbid conditions), and high multi-morbidity (≥6 comorbid conditions). Association between multi-morbidity and clinical outcomes were analyzed by treatment with a median follow-up of 1.8 (1.3–2.3) years.

Results Multi-morbidity was present in 64% (n = 10,713) of patients; 51% (n = 8491) had moderate multi-morbidity, 13% (n = 2222) had high multi-morbidity, and 36% (n = 6087) had no multi-morbidity. Compared with the no multi-morbidity group, the high multi-morbidity group was older (74 vs 69 years), took twice as many medications (10 vs 5), and had higher CHA_2DS_2-VASc scores (4.9 vs 2.7) (all $P < .001$). Adjusted rates per 100 patient-years for stroke/systemic embolism, death, and major bleeding increased with multi-morbidity (Reference no multi-morbidity; moderate multi-morbidity 1.42 [1.24–1.64] and high multi-morbidity 1.92 [1.59–2.31]), with no interaction in relation to efficacy or safety of apixaban.

Conclusions Multi-morbidity is prevalent among the population with AF; efficacy and safety of apixaban is preserved in this subgroup supporting extension of trial results to the most complex AF patients. (Am Heart J 2019;208:123-31.)

Atrial fibrillation (AF) is largely a condition of aging. Most patients with AF are older than 70 years and have other chronic health conditions.[1] Anticoagulation is highly effective in the prevention of stroke and embolic events [2] but it increases the risk of major bleeding. Clinical trials typically test the efficacy and safety of a particular drug in healthier cohorts without multiple chronic conditions or polypharmacy.[3] Particularly for frail older patients, concerns about using anticoagulation may increase due to a higher risk of bleeding, concomitant medications (antiplatelet therapy, nonsteroidal anti-inflammatory drugs, other medications which share a common metabolic or elimination pathway), and complicating factors such as risk of falls.[4] Cumulative comorbidity counts provide a proxy for identifying frailty, chronic disease burden and functional status.[5] Specifically, greater comorbidity increases the demands on regulation of physiological processes and resilience.

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial demonstrated superior efficacy and safety of apixaban as compared with warfarin in patients with

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Brian Olshansky, MD served as guest editor for this article.
Clinical trial registration: ClinicalTrials.gov (NCT00412984).
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0002-8703

https://doi.org/10.1016/j.ahj.2018.09.017

AF.[6,7] The trial results were the same across pre-specified subgroups, including those defined by single comorbidities (diabetes, heart failure or age).[8-10] Patients with AF and a history of falls also have a higher risk of bleeding and death with anticoagulation, with a consistent efficacy and safety of apixaban.[11] However, data are lacking about use of oral anticoagulants in trial populations with multiple comorbid conditions. We describe the prevalence of multi-morbidity in ARISTOTLE, defined as ≥3 comorbid conditions, and determine the association between multi-morbidity and outcomes, specifically assessing the efficacy and safety of apixaban as compared with warfarin.

Methods

ARISTOTLE trial

The design and main results of the ARISTOTLE trial (NCT00412984) have been reported.[6,7] In brief, ARISTOTLE was a multicenter, double-blind trial comparing apixaban with warfarin performed between 2006 and 2011. Patients with documented AF or atrial flutter were eligible for inclusion if ≥1 of the following risk factors for thromboembolism were present: symptomatic heart failure within 3 months before inclusion or left ventricular ejection fraction ≤40%; hypertension requiring pharmacologic treatment; age ≥75 years; diabetes mellitus; and prior stroke, transient ischemic attack, or systemic embolus. Exclusion criteria included clinically significant mitral stenosis, conditions other than AF requiring anticoagulation, required aspirin treatment >165 mg/day or used in combination with a thienopyridine, recent ischemic stroke, AF due to reversible causes, increased bleeding risk considered to be a contraindication to oral anticoagulation, and severe renal insufficiency (creatinine clearance <25 mL/min). Patients were randomized to receive apixaban 5 mg twice daily (n = 9120) or dose-adjusted warfarin (n = 9081) with a target international normalized ratio of 2.0–3.0. A reduced dose of apixaban 2.5 mg twice daily or matching placebo was used for those patients with ≥2 of the following criteria at baseline: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. All patients provided informed consent, and the protocol was approved by ethics committees at participating sites.

Population

For this analysis, ARISTOTLE participants age ≥55 years were included (n = 16,800). The population for this analysis excluded younger patients (<55 years; 4% of the trial population) to preserve a clear relationship between multi-morbidity and age-associated declines. Baseline comorbidities included coronary artery disease (prior myocardial infarction, history of percutaneous coronary intervention/coronary artery bypass grafting), congestive heart failure, moderate/severe valvular heart disease, hypertension requiring pharmacologic treatment, peripheral vascular disease (peripheral artery disease, aortic aneurysm), cerebrovascular disease (carotid stenosis, transient ischemic attack, stroke), emotional or cognitive impairment (depression, antidepressant use, dementia), pulmonary disease (chronic obstructive pulmonary disease, asthma), obstructive sleep apnea, gastrointestinal disease (dyspepsia, gastroesophageal reflux disease, peptic ulcer disease), chronic liver disease, hypo/hyperthyroidism, diabetes with and without complications, musculoskeletal disorder (previous non-traumatic falls within last year, osteoporosis), chronic kidney disease (creatinine clearance <50 mL/min), hematological disorder (history of anemia or hemoglobin <10 g/dL), and malignancy other than basal or squamous cell skin cancer (Table I). Distribution of comorbidity counts are shown across the population (Figure 1). Participants were placed in 3 groups according to the number of these 17 comorbidities: 0–2 comorbidities (no multi-morbidity group), 3–5 comorbidities (moderate multi-morbidity group), and ≥6 comorbidities (high multi-morbidity group).

Outcomes

The primary efficacy outcome was stroke or systemic embolism. The primary safety outcome was major bleeding according to the International Society on Thrombosis and Hemostasis (ISTH) criteria, which includes any clinically overt bleeding event accompanied by ≥1 of the following: hemoglobin drop of ≥2 g/dL or transfusion of ≥2 units of packed red blood cells, bleeding at a critical site (intracranial, intraspinal, intraocular, intraarticular, pericardial, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding.[12] Secondary efficacy endpoints included stroke, death, and myocardial infarction; secondary safety endpoints included intracranial bleeding, ISTH major or clinically relevant nonmajor (CRNM) bleeding, and any bleeding. Net clinical benefit endpoints included stroke, systemic embolic events, major bleeding, and death.

Statistical analysis

Baseline characteristics are shown for the multi-morbidity groups (no multi-morbidity [0–2 comorbidities], moderate [3–5], and high [≥6]). Continuous variables are presented as medians and 25th, 75th percentiles, and categorical variables are presented as counts and proportions. P-values comparing groups were computed using the Kruskal-Wallis test or ANOVA for continuous variables and the chi-square test for categorical variables. Event rates for each clinical outcome were computed as the number of events per 100 patient-years of follow-up. A Cox proportional hazards model was used to assess the association between multi-morbidity groups and clinical outcomes. The proportional hazards assumption was not violated for any outcome. The association between clinical outcomes and group (reference group:

Table I. Seventeen qualifying comorbidities: prevalence across multi-morbidity groups.

Comorbidity	No Multi-morbidity* (n = 6087)	Moderate Multi-morbidity† (n = 8491)	High Multi-morbidity‡ (n = 2222)
CAD (CAD, prior MI, PCI/CABG)	786 (12.9)	3861 (45.5)	1606 (72.3)
Heart failure	639 (10.5)	2813 (33.2)	1142 (51.4)
Valvular disease	290 (4.8)	1768 (20.8)	964 (43.4)
Hypertension	4806 (79.2)	7688 (90.6)	2102 (94.6)
PVD (PAD or aortic aneurysm)	56 (0.9)	503 (5.9)	502 (22.9)
CVD (carotid stenosis, TIA, stroke)	465 (7.6)	1576 (18.6)	764 (34.4)
Depression or Dementia§	116 (1.9)	834 (9.8)	666 (30.0)
Dementia	5 (0.1)	49 (0.6)	42 (1.9)
Depression	112 (1.8)	799 (9.4)	632 (28.4)
Pulmonary (COPD, asthma)	210 (3.4)	1369 (16.1)	846 (38.1)
Sleep apnea	61 (1.0)	485 (5.7)	373 (16.8)
GI disorder (dyspepsia, GERD, PUD)	341 (5.6)	2050 (24.1)	1160 (52.2)
Chronic liver disease	23 (0.4)	246 (2.9)	173 (7.8)
Hypo- or hyperthyroidism	198 (3.3)	1109 (13.1)	630 (28.4)
Diabetes	637 (10.5)	2449 (28.8)	1095 (49.3)
Musculoskeletal (falls, osteoporosis)	211 (3.5)	998 (11.8)	633 (28.5)
Renal (CKD or CrCl <50 mL/min)	405 (6.7)	2185 (25.7)	1131 (50.9)
Anemia (Hgb <10 g/dL)	203 (3.3)	1602 (18.9)	1063 (47.8)
Malignancy (other than skin cancer)	142 (2.3)	657 (7.7)	424 (19.1)

Data presented as no. (%).
CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; CVD = cardiovascular disease; GERD = gastroesophageal reflux disease; Hgb = hemoglobin; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PUD = peptic ulcer disease; PVD = peripheral vascular disease; TIA = transient ischemic attack.
* 0–2 comorbidities.
† 3–4 comorbidities.
‡ ≥6 comorbidities.
§ History of depression, antidepressant use, dementia.

no multi-morbidity group [0–2 comorbidities]) was tested in both unadjusted models and models adjusted for sex, age, race, and region. A limited adjustment was selected to preserve the association between comorbidity and outcomes, and interaction between treatment and multi-morbidity group was tested in the model for outcomes. Hazard ratios comparing apixaban with warfarin for each group were computed and interaction terms tested.

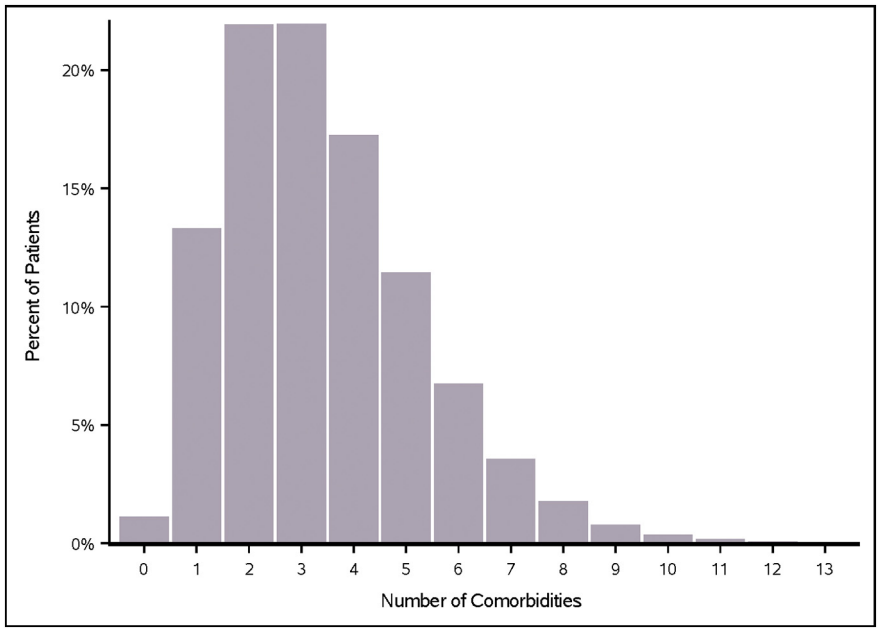
Finally, the association between the number of comorbidities on a continuous scale and major bleeding was tested using a Cox proportional hazards model, with and without an interaction between the number of comorbidities and treatment arm. The comorbidity variable demonstrated linearity in relation to the major bleeding outcome, and the hazard ratios (HR) with 95% confidence intervals (CI) per 1 comorbidity increase and p-values are presented.

Two-sided p-values ≤0.05 were considered statistically significant. All analyses were performed by the Duke Clinical Research Institute (Durham, NC) using SAS version 9.4 (SAS Institute, Inc., Cary, NC). The ARISTOTLE trial was funded by Bristol-Myers Squibb and Pfizer. The authors are solely responsible for all analyses which were conducted at the Duke Clinical Research Institute, as well as the drafting and editing of the paper and its final contents. The sponsor played no role in the decision to submit the manuscript for publication.

Results

Overall, 64% of the population had multi-morbidity, defined as ≥3 comorbid conditions; 51% (n = 8491) had moderate multi-morbidity (3–5 comorbidities), 13% (n = 2222) had high multi-morbidity (≥6 comorbidities), and 36% (n = 6087) had no multi-morbidity (0–2 comorbidities). The distribution of comorbidities by group is shown in Table I. Common comorbidities were hypertension, coronary artery disease, heart failure, and diabetes. All comorbidities showed an increase in prevalence across multi-morbidity groups, with notable increases in gastrointestinal disorders, diabetes, chronic kidney disease, and anemia, and a more consistent and high rate of hypertension across groups. Compared with moderate and no multi-morbidity groups, the high multi-morbidity group was older (74 [high] vs 71 [moderate] and 69 [no] years), more often female, and had higher CHA_2DS_2-VASc (4.9 vs 3.8 and 2.7) and HAS-BLED (1.6 vs 1.9 vs 2.4) scores (Table II). Other conditions associated with aging were more common in the high multi-morbidity group, including falls in the past year (11.3%), cognitive/emotional issues (30.0%), low body

Figure 1



Distribution of comorbidity counts across the population.

mass index <22 kg/m^2 (8.1%), and polypharmacy (95.2% taking ≥5 medications) (all $P < .001$). Medication use increased in the high multi-morbidity group, including more antiplatelet therapy (38.0%), nonsteroidal anti-inflammatory drugs (14%), and gastric acid reducers (37%).

Clinical outcomes according to multi-morbidity

Outcomes were assessed across groups during a median follow-up of 1.8 years (25th, 75th percentiles: 1.3, 2.3 years). The event rates per 100 patient-years and adjusted HRs with 95% CIs and *P* values for each group as compared with the no multi-morbidity group are presented in Table III. The risk of stroke/systemic embolism, ischemic stroke, myocardial infarction, death, bleeding endpoints (major, major/CRNM, or any bleeding), and net benefit endpoints were increased for high and moderate multi-morbidity groups compared with no multi-morbidity group. Particularly notable was the more than 3-fold increased risk of death and myocardial infarction among the high multi-morbidity group. HRs remained significant after adjustment (Figure 2).

Effect of apixaban versus warfarin according to multi-morbidity

There were no interactions between multi-morbidity group and treatment, with a favorable profile of apixaban as compared with warfarin consistent with the main trial results (eTable 1). There was a trend toward less intracranial hemorrhage with apixaban among the high multi-morbidity group as compared with the no multi-morbidity group (HR 0.28 vs 0.61; p interaction = 0.10) (Figure 3).

The risk of major bleeding increased by about 15% for every 1 comorbidity increase (adjusted HR 1.14, 95% CI 1.09–1.18; $P < .0001$). The hazard ratio for major bleeding with apixaban versus warfarin remains significant in favor of apixaban within each selected comorbidity level (e.g., with exactly 1 comorbidity: major bleeding HR 0.58, 95% CI 0.45–0.75; with exactly 3 comorbidities: major bleeding HR 0.66, 95% CI 0.56–0.77; with exactly 6 comorbidities: major bleeding HR 0.78, 95% CI 0.64–0.97). There was no significant interaction between comorbidity as a continuous variable and treatment arm (p interaction = 0.10) with a benefit of apixaban as compared with warfarin across the different number of comorbidities. The correlation between number of drugs (polypharmacy) and number of conditions (multi-morbidity) was weak (test for correlation = 0.48). There was no interaction between polypharmacy and multi-morbidity for the outcome of major bleeding (*P* interaction = .30).

Discussion

The majority of the ARISTOTLE population had multiple chronic conditions; 13% are the most complex with ≥6 comorbid conditions. Greater multi-morbidity is associated with an increased risk of death, myocardial infarction, and stroke/systemic embolism before and after adjustment; major bleeding increased by 15% with each

Table II. Baseline demographics by comorbidity groups.

	No Multi-morbidity* (n = 6087)	Moderate Multi-morbidity† (n = 8491)	High Multi-morbidity‡ (n = 2222)
Age, median (25th, 75th), y	69 (63, 75)	71 (65, 77)	74 (68, 79)
Female sex, no. (%)	1894 (31.1)	3261 (38.4)	909 (40.9)
Persistent AF (vs paroxysmal), no. (%)	5313 (86.5)	7134 (84.3)	1825 (83.1)
Region, no. (%)			
North America	925 (15.2)	2217 (26.1)	1079 (48.6)
Latin America	1643 (27.0)	1443 (17.0)	151 (6.8)
Europe	2336 (38.4)	3638 (42.8)	795 (35.8)
Asia Pacific	1183 (19.4)	1193 (14.1)	197 (8.9)
History of fall in past year, no. (%)	138 (2.6)	360 (4.6)	240 (11.3)
BMI <22 kg/m^2, no. (%)	374 (6.2)	647 (7.7)	180 (8.1)
Systolic BP, median (25th, 75th), mm Hg	130 (120, 141)	130 (120, 140)	130 (118, 140)
CHA_2DS_2-VASc score ≥3, no. (%)	80 (1.3)	885 (10.4)	760 (34.2)
CHA_2DS_2-VASc score, mean (SD)	2.7 (1.1)	3.8 (1.4)	4.9 (1.4)
HAS-BLED score	1.6 (0.9)	1.9 (1.0)	2.4 (1.1)
Antiplatelet (aspirin or clopidogrel), no. (%)	1681 (27.6)	2949 (34.7)	926 (42.2)
NSAID use, no. (%)	397 (6.7)	754 (9.0)	317 (14.3)
Gastric antacid, no. (%)	668 (11.3)	1693 (20.2)	822 (37.2)
ACE inhibitor or ARB, no. (%)	3941 (66.4)	245 (74.3)	1703 (77.1)
Beta-blocker, no. (%)	3567 (60.1)	5436 (64.7)	1551 (70.2)
Calcium channel blocker, no. (%)	1701 (28.7)	2761 (32.9)	797 (36.1)
Digoxin, no. (%)	1724 (29.0)	2806 (33.4)	778 (35.2)
At least 5 drugs, no. (%)	3762 (61.8)	7117 (83.8)	2115 (95.2)

All $P < .001$.
ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; NSAID = nonsteroidal anti-inflammatory drugs.
*0–2 comorbidities.
†3–4 comorbidities.
‡≥6 comorbidities.

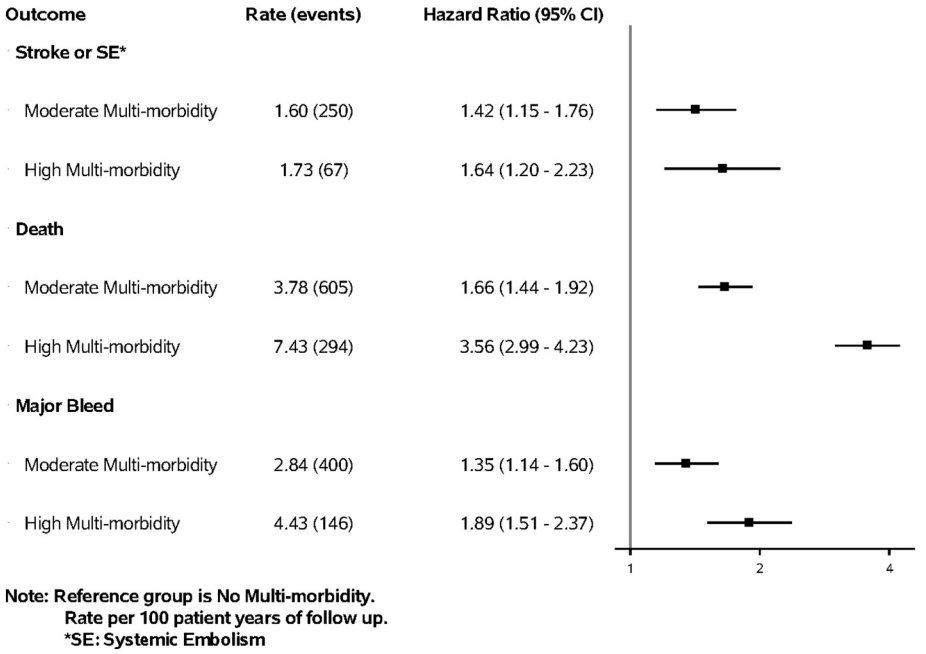
Table III. Adjusted HR of efficacy and safety endpoints per 100 patient-years per groups (REF: No multi-morbidity [0–2 comorbidities]).

	No Multi-morbidity*	Moderate Multi-morbidity†			High Multi-morbidity‡		
Endpoint	Rate (Count)	Rate (Count)	Adj§ HR (95% CI)	*P*	Rate (Count)	Adj§ HR (95% CI)	*P*
Efficacy endpoints							
Stroke or SE	1.21 (137)	1.60 (250)	1.42 (1.15–1.76)	.001	1.73 (67)	1.64 (1.20–2.23)	.002
Ischemic stroke	0.73 (83)	1.18 (184)	1.71 (1.31–2.22)	<.0001	1.34 (52)	2.04 (1.417–2.95)	.0001
Hemorrhagic stroke	0.39 (44)	0.37 (59)	1.11 (0.74–1.65)	.62	0.23 (9)	0.78 (0.37–1.65)	.52
MI	0.33 (38)	0.57 (90)	1.55 (1.06–2.28)	.03	1.37 (53)	3.15 (2.03–4.91)	<.0001
Death	2.55 (295)	3.78 (605)	1.66 (1.44–1.92)	<.0001	7.43 (294)	3.56 (2.99–4.23)	<.0001
Safety Endpoints							
Major bleed	2.05 (215)	2.84 (400)	1.35 (1.14–1.60)	.0005	4.43 (146)	1.89 (1.51–2.37)	<.0001
Major/CRNM bleed	4.02 (415)	5.36 (740)	1.30 (1.15–1.47)	<.0001	8.10 (260)	1.78 (1.51–2.10)	<.0001
Intracranial bleed	0.64 (68)	0.57 (82)	0.95 (0.68–1.31)	.74	0.53 (18)	0.91 (0.53–1.57)	.73
Any bleed	18.75 (1644)	22.31 (2580)	1.17 (1.10–1.24)	<.0001	34.68 (872)	1.62 (1.48–1.77)	<.0001
Net Benefit							
Stroke/SE/Major bleed	2.82 (314)	4.00 (610)	1.42 (1.24–1.64)	<.0001	5.78 (215)	1.92 (1.59–2.31)	<.0001
Stroke/SE/Major bleed/Death	4.82 (538)	7.03 (1074)	1.546 (1.391–1.718)	<.0001	12.08 (450)	2.657 (2.323–3.039)	<.0001

*0–2 comorbidities. †3–4 comorbidities. ‡≥6 comorbidities.
Rates computed as number of events per 100 patient-years of follow-up. Hazard ratio compares groups to 0–2 comorbidities group.
§Adjusted for age, sex, race, and region. Ischemic stroke includes uncertain stroke type.
CI = confidence interval; CRNM = clinically relevant nonmajor; HR = hazard ratio; SE = systemic embolism.

additional comorbidity. Despite the higher bleeding risk, outcomes favoring apixaban over warfarin were preserved. As the high multi-morbidity group included patients with cognitive issues, polypharmacy, gastrointestinal disorders, and falls, the preserved efficacy and safety of apixaban over warfarin in this most complex

Figure 2



Adjusted HR of adverse events in the moderate and high multi-morbidity groups compared with those with the no multi-morbidity group.

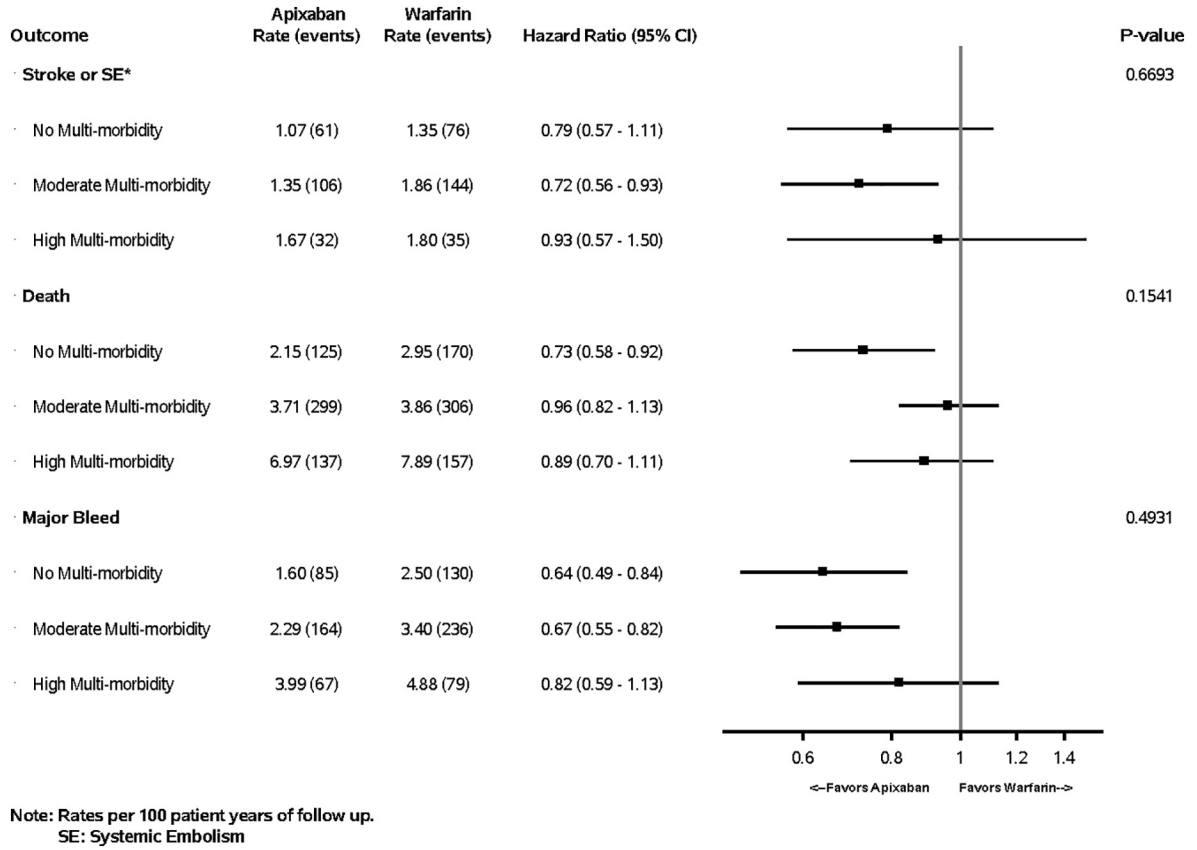
subgroup suggests results can be safely extended to similar patients in clinical practice.

In AF registries, older age and comorbidity are predictive of mortality, stroke, and bleeding events over time.[13] Large AF registries, such as GARFIELD-AF and ORBIT-AF, enroll high risk populations, yet according to one review, just 60% would meet ARISTOTLE inclusion criteria.[14] The high multi-morbidity group in ARISTOTLE is a vulnerable group more similar to those enrolled in registries, but treatment is based on randomization. For example, the median CHA_2DS_2-VASc score in ORBIT-AF is 4 compared with a median score of 4.9 in the high multi-morbidity (≥6 comorbidities) subgroup in ARISTOTLE.[15] Multi-morbidity reflects age-associated risk based on a cumulative deficit approach. While some with multi-morbidity will be phenotypically frail, and some will not, cumulative comorbidity is a reliable proxy for vulnerability to adverse outcomes.[5] This cumulative deficit approach has been applied using counts from claims data or electronic health records.[16-18] Comorbid conditions summed without ranking summarize stress on physiologic homeostasis. The ability to study frail patients in clinical trials is challenging due to the enrollment of healthier populations and difficulty implementing performance-based measures and scores; a cumulative deficit approach provides an attractive alternative. The use of apixaban in a registry may seem safe and efficacious, but there is always provider's choice in who gets drugs compared to who does not. Patients with multimorbidity often receive no oral anticoagulation, or providers hesitate to prescribe a novel oral anticoagulant. Therefore, this analysis on a non-pre-specified subgroup provides a higher quality of evidence due to inherent monitoring, quality criteria and endpoint assessment in a trial. Most importantly, use of apixaban or warfarin was randomized which is of particular relevance to those with the highest comorbidity burden. We consider the confirmation of the efficacy and safety of apixaban over warfarin in the subgroup in ARISTOTLE with the greatest comorbidity burden informative for decision making regarding anticoagulation for atrial fibrillation.

Multiple chronic conditions are a driver of polypharmacy. In a prior analysis, polypharmacy did not alter the efficacy and safety of apixaban and showed similar results favoring apixaban in the greatest polypharmacy group.[19] Simplifying the drug regimen is important for those with multiple conditions. In our analysis, the group with the greatest number of comorbidities was on more nonsteroidal anti-inflammatory drugs and antiplatelet therapy than those with fewer comorbidities. Polypharmacy speaks to concerns related to drug–drug and drug-host interactions. However, distinct from prescribing practices, comorbidity counts reflect of complexity and vulnerability to adverse outcomes.[16] We found no interaction between multi-morbidity and polypharmacy for major bleeding.

Patients with multiple chronic conditions are also consumers of health care resources and contribute to health care costs.[1] In addition to a higher risk of death,

Figure 3



HR of outcomes in each multi-morbidity group with apixaban compared with warfarin.

patients with multiple chronic conditions have higher rates of hospitalization and outpatient visits. From the UK Biobank analysis, the level of multi-morbidity was strongly associated with survival in older adults with AF making this group particularly relevant for targeted interventions.[20] Preventable events in this population provide cost savings. A Medicare analysis found that older patients with AF starting apixaban had lower total health care costs due to less bleeding and stroke-related care as compared with warfarin, despite higher medication costs.[21] According to the ORBIT-AF registry, three-quarters of patients with new AF are started on a non-vitamin K antagonist oral anticoagulant.[22] The most frequent reason among those with no anticoagulant for stroke prevention was patient refusal, followed by a history of falls or frailty.[23] These results demonstrate that bleeding, frailty and falls continue to be a concern when making decisions about anticoagulation. We found that apixaban-treated patients with high multi-morbidity (≥6 chronic conditions) had a favorable benefit from apixaban as compared with warfarin, likely resulting in less bleeding and associated health care expenditures. These data support the efficacy and safety of apixaban in this group with higher overall costs of care.

Limitations

This post hoc analysis was not pre-specified, so limitations apply. Comorbidity counts were limited to those collected on the case report form, leading to a potential misclassification of comorbidity burden due to unreported comorbidities. Comorbidities were not confirmed or graded by severity, and non-cardiovascular and cardiovascular comorbidities were equal contributors. Comorbidities vary in the hazard they pose, however our purpose was to describe the accumulation of deficits (comorbidities) rather than assess the individual risk of a comorbidity. Cumulative deficits suggest the presence of frailty but is not the same as phenotypic frailty assessed by strength, function, nutrition, and activities of daily living (unavailable). Other comorbidity scores, like the Charlson Comorbidity Index, select specific comorbidities and provide weights. Unlike these comorbidity scores, cumulative deficit is a summation approach which does not weight one comorbid condition over another. Finally, while the

intention of the trial was to evaluate the efficacy and safety of apixaban compared with warfarin in relation to key bleeding and embolic events, outcomes of value to participants with the greatest degree of multi-morbidity may differ, such as preserving function at the lowest possible cost.

Conclusion

Multi-morbidity occurs in two-thirds of a contemporary trial population with AF, and is associated with older age, cognitive declines, polypharmacy, falls in the prior year, and an increased risk of bleeding and stroke. Although multi-morbidity is associated with a greater risk of stroke or systemic embolism, death, and major bleeding, the efficacy and safety of apixaban compared with warfarin were preserved in this high-risk population. This lends support to the use of apixaban for stroke prevention in atrial fibrillation among vulnerable patients with multi-morbidity.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.09.017.

Acknowledgements

The ARISTOTLE trial was funded by Bristol-Myers Squibb and Pfizer.

All analyses were conducted at the Duke Clinical Research Institute (DCRI, Durham, NC) and all authors had full access to all data. The DCRI coordinate the trial and managed the database. An academic steering committee designed the trial and was responsible for oversight of study conduct, reporting of all results, and takes responsibility for the accuracy and completeness of the data analyses. The authors are fully responsible for the study design, data collection, analysis and interpretation of the data, and writing of the manuscript. All authors agreed to submit the manuscript for publication. The sponsor played no role in the decision to submit the manuscript for publication.

Conflict of Interest Disclosures

K.P. Alexander, Mulder, Al-Khatib: None. Brouwer: Consulting fees/honoraria: AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo. Vinereanu: Research grant: GlaxoSmithKline, Pfizer, Bristol-Myers Squibb. Lopes: Research grant: Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer; Consultant/Advisory Board: Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Merck, Portola, GlaxoSmithKline, Pfizer. Proietti: Consultant: Boehringer Ingelheim. Hijazi: Honoraria: Boehringer Ingelheim, Roche Diagnostics, Pfizer and Bristol-Myers Squibb; Consultant/Advisory board: Pfizer, Bristol-Myers Squibb, Roche Diagnostics, and Merck, Sharp & Dohme. Halvorsen: To be provided. Hylek: Consultant: Bayer, Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, Janssen, Medtronic, Portola; Research grant: Bristol Myers Squibb/Pfizer, Janssen.

Verheugt: Honoraria/Consultant: Bayer Healthcare, Boehringer-Ingelheim, BMS/Pfizer, and Daiichi-Sankyo. J.H. Alexander: Institutional research grants from Bristol-Myers Squibb, Boehringer Ingelheim, CryoLife, CSL Behring, the US Food and Drug Administration, the National Institutes of Health, Tenax Therapeutics, and VoluMetrix; consulting fees/honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen Pharmaceuticals, Merck, Novo Nordisk Pharmaceuticals, Pfizer, Portola Pharmaceuticals, VA Cooperative Studies Program, and Zafgen. Wallentin: Institutional research grants from Bristol-Myers Squibb/Pfizer, AstraZeneca, Merck, Boehringer Ingelheim, and GlaxoSmithKline; consulting fees from GlaxoSmithKline, Bristol-Myers Squibb/Pfizer, Abbott, AstraZeneca, and Boehringer Ingelheim.

Granger: Research Grant: Armetheon, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, GlaxoSmithKline, Janssen, Medtronic Foundation, Novartis, Pfizer, The Medicines Company; Consultant/Advisory Board: AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Gilead Sciences, Inc., GlaxoSmithKline, Hoffman LaRoche, Janssen, Medtronic, Novartis, Pfizer, The Medicines Company, Verseon.

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