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ORIGINAL ARTICLE
Atrial fibrillation

Antithrombotic therapy use and clinical outcomes following thrombo-embolic events in patients with atrial fibrillation: insights from ARISTOTLE

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Aims We investigated baseline characteristics, antithrombotic use, and clinical outcomes of patients with atrial fibrillation (AF) and a thrombo-embolic event in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study to better inform the care of these high-risk patients.

Method and results Thrombo-embolic events were defined as stroke (ischaemic or unknown cause) or systemic embolism (SE). Clinical outcomes were estimated using the Kaplan–Meier method. All-cause mortality and International Society on Thrombosis and Haemostasis (ISTH) major bleeding after events were analysed using a Cox proportional hazards model with time-dependent covariates. Of 18 201 patients in ARISTOTLE, 365 experienced a thrombo-embolic event [337 strokes (ischaemic or unknown cause), 28 SE]; 46 (12.6%) of which were fatal. In the 30 days before and after a thrombo-embolic event, 11% and 37% of patients, respectively, were not taking an oral anticoagulant. During follow-up (median 1.8 years), 22 patients (7.1%/year) had a recurrent stroke, 97 (30.1%/year) died, and 10 (6.7%/year) had major bleeding. Compared with patients without a thrombo-embolic event, the short- and long-term adjusted hazards of death in patients with a thrombo-embolic event were high [≤30 days: hazard ratio (HR) 54.3%, 95% confidence interval (95% CI) 41.4–71.3; >30 days: HR 3.5, 95% CI 2.5–4.8; both $P < 0.001$]. The adjusted hazards of major bleeding were also high short-term (HR 10.37, 95% CI 3.87–27.78; $P < 0.001$) but not long-term (HR 1.7, 95% CI: 0.77–3.88; $P = 0.18$).

Conclusions Thrombo-embolic events were rare but associated with high short- and long-term morbidity and mortality. Substantial numbers of patients are not receiving oral anticoagulattherapy before and, despite this risk, after a first thrombo-embolic event.

Clinical Trial Registration ClinicalTrials.gov (NCT00412984).

Keywords Antithrombotic therapy • Thrombo-embolic events • Atrial fibrillation

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Introduction

Atrial fibrillation (AF), a common arrhythmia, is related to a high incidence of stroke.[1–4] Vitamin K antagonists (VKAs), such as warfarin, reduce the risk of stroke; however, their use is limited by the need for routine monitoring and food and drug interactions.[3–6] Several direct-acting oral anticoagulants are now available for use as an alternative to warfarin and recommended in practice Guidelines.[7–11] The results of the (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study demonstrated that the factor Xa inhibitor apixaban was superior to warfarin for the prevention of stroke and systemic embolism (SE), caused less bleeding, and resulted in lower mortality in patients with AF.[8] Despite effective oral anticoagulation, patients with AF are still at risk for thrombo-embolic events, including stroke and systemic embolism. We investigated the baseline characteristics, antithrombotic therapy use, and subsequent clinical outcomes of patients who experienced a thrombo-embolic event in the ARISTOTLE study to better inform the care of this high-risk cohort of patients.

Methods

The design and primary results of the ARISTOTLE trial have been reported previously.[8,12] Briefly, 18 201 patients with AF and at least one risk factor for stroke were randomly assigned to receive apixaban 5 mg twice daily (2.5 mg twice daily in patients with two or more of the following: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine concentration ≥ 1.5 mg/dL) or warfarin adjusted to achieve a target international normalized ratio of 2.0–3.0. The median duration of follow-up was 1.8 years. The primary endpoint was stroke or SE; secondary endpoints included major bleeding and death from any cause. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria as clinically overt bleeding accompanied by a decrease in haemoglobin of ≥2 g/dL or transfusion of ≥2 units of packed red cells, occurring at a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), or resulting in death.[13] Patients were excluded if they had conditions other than AF that required anticoagulation, stroke within the previous 7 days, need for aspirin >165 mg a day or need for both aspirin and clopidogrel, and creatinine clearance <25 mL/min.[8]

Study population, design, and outcomes

All patients in the ARISTOTLE study were included in this analysis. We compared patients who experienced a thrombo-embolic event during the study period with those who did not. Thrombo-embolic events were defined as stroke classified as ischaemic or of uncertain cause and SE. We describe the characteristics of thrombo-embolic events, compare the baseline characteristics of patients with and without thrombo-embolic events, describe antithrombotic therapy use before and after thrombo-embolic events, and report rates of recurrent stroke or SE, death, and bleeding following a thrombo-embolic event. Institutional review board approval of the study protocol was obtained at all sites, and all patients provided written informed consent.

Use of study drug around thrombo-embolic events

Information about permanent and temporary discontinuations of study drug was collected during the course of the study as the discontinuations occurred. Study drug compliance was calculated by dividing the total number of pills taken by the number of pills expected to be taken by the patient. Expected pill counts are based on the total number of days the patient was in the study and did not discontinue study drug. The actual number of pills taken by a patient was calculated based on the pill counts of returned study drug containers. Being on/off study drug in the period around a thrombo-embolic event was defined as receiving study drug at least once in the period before or after the event. There was no specific guidance in the study protocol about the treatment of patients who experienced a thrombo-embolic event other than recommending that patients restart oral anticoagulant therapy (either assigned study drug or open-label warfarin) when clinically appropriate.

Statistical analysis

Continuous variables are summarized as medians and 25th, 75th percentiles and categorical variables as frequencies and percentages. Differences between the two groups were tested using a Kruskal-Wallis test for continuous variables and a χ^2 test or Fisher's mid-p for categorical variables. Baseline characteristics are presented for patients who experienced a thrombo-embolic event and those who did not.

To identify the use of anticoagulant therapy before and after thrombo-embolic events, information regarding the use of anticoagulant therapy (study drug, open-label warfarin, dabigatran, aspirin, clopidogrel) at 1, 7, and 30 days before and 3, 14, and 30 days after thrombo-embolic events was captured. Thrombo-embolic events that occurred while on study drug were defined as events occurring in patients receiving study drug the day before the event. Study drug interruption is defined as not receiving study drug on the day of and at least 1 of 3 days after the thrombo-embolic event. Study drug resumption is defined as receiving study drug on at least 1 day following interruption.

The clinical outcomes of patients who experienced a thrombo-embolic event and those who did not were estimated using the Kaplan–Meier method; curves comparing the estimated probability of the endpoints of all-cause death and major bleeding after a thrombo-embolic event were created with the date of the thrombo-embolic event set as Day 0. The number of deaths, major bleeding events, and recurrent stroke after thrombo-embolic events as well as event rates per 100 patient-years are reported.

Death and major bleeding after the thrombo-embolic event were analysed using a Cox proportional hazards model with time-dependent variables for thrombo-embolic events (0 = no event, 1 = event within the past 30 days, 2 = event more than 30 days ago) and covariate adjustments for mortality including age, sex, region, systolic/diastolic blood pressure, weight, hypertension, moderate valvular disease, left bundle branch block on electrocardiogram, prior myocardial infarction, prior stroke/transient ischaemic attack/SE, anaemia, smoking, prior VKA use, New York Heart Association classification, all components of the $CHADS_2$ score, and renal function. Adjustment covariates for serious bleeding included age, sex, region, coronary artery disease, prior myocardial infarction, prior bleeding, anaemia, all components of the $CHADS_2$ score, and renal function. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Location and severity of thrombo-embolic events

There were total of 365 thrombo-embolic events during the ARISTOTLE trial. The majority of the thrombo-embolic events were strokes of ischaemic or unknown cause [$n = 337$ (92.3%)] (*Table 1*).

Table 1 Characteristics of first thrombo-embolic event

Characteristics	Number of events (%)
Stroke: ischaemic or unknown cause	337/365 (92.3)
Rankin score	
0	28/210 (13.3)
1	49/210 (23.3)
2	41/210 (19.5)
3	29/210 (13.8)
4	30/210 (14.3)
5	21/210 (10.0)
6	12/210 (5.7)
Severity of stroke deficit	
None	77/332 (23.2)
Minor	77/332 (23.2)
Moderate	81/332 (24.4)
Severe	54/332 (16.3)
Death	43/332 (13.0)
Result of traumatic injury	11/329 (3.3)
Systemic embolism	28/365 (7. 7)
Result in death	3/27 (11.1)
Location	
Extremity	21/27 (77.78)
Renal	2/27 (7.41)
Splenic	0/27 (0)
Mesenteric	2/27 (7.41)
Other	2/27 (7.41)

Among those with stroke, 77 (23.2%) were classified as having no neurological deficit, 77 (23.2%) had minor deficit, 81 (24.4%) had moderate deficit, 54 (16.3%) had severe deficit, and 43 (12.8%) were classified as fatal. A total of 28 (7.7%) patients experienced SE; fatal SE occurred in 3 (11.1%) patients.

Patient characteristics

Patients who experienced a thrombo-embolic event were slightly older, had lower body weight, higher incidence of previous myocardial infarction, more persistent AF, less previous VKA use, and worse renal function than those who did not experience a thrombo-embolic event (*Table 2*). With the exception of anticoagulant therapy, medication use at baseline was similar among patients who experienced a thrombo-embolic event compared with those who did not. The reduced dose of apixaban (2.5 mg twice daily) was used in 26 (7.1%) patients due to baseline dose reduction criteria. Patients who experienced a thrombo-embolic event had a slightly higher $CHADS_2$ score (2.6 vs. 2.1) than those who did not.

Antithrombotic therapy

A total of 117 (32.1%) patients who experienced a thrombo-embolic event did not receive study drug the day before the event. Data describing the reasons patients stopped drug are available for 76 of the 117 patients; a total of 87 reasons were provided. Reasons for stopping study drug were due to bleeding [5 (5.7%)], other adverse events [23 (26.1%)], emergency procedures [8 (9.1%)], elective procedures [11 (12.5%)], patient request [11 (12.5%)], physician decision [11 (12.5%)], and other unspecified reasons [18 (20.5%)]. Only 87% received study drug at least once within the 30 days before event (*Table 3*). Overall, study drug compliance based on pill count in the group of patients experiencing thrombo-embolic events was 96.3% and not markedly different from compliance among those not experiencing a thrombo-embolic event (97.6%).

After a thrombo-embolic event, use of study drug, defined as 'receiving study drug at least once in the 3, 14, and 30 days after the event,' was even lower than before events and did not reach 60% at 30 days after the thrombo-embolic event. Only five patients received thrombolytic therapy within a week of a thrombo-embolic event and only 116 received a parenteral anticoagulant.

Roughly 25% of patients who experienced a thrombo-embolic event were taking open-label aspirin, most in combination with study drug. Open-label VKA, clopidogrel, and aspirin use was higher after a thrombo-embolic event. Study drug was interrupted at or just after the thrombo-embolic event in 147 (59.3%) patients; 43 patients resumed study drug a median of 13 (7, 30) days after the event (*Table 4*).

Clinical outcomes

The rate of death was substantially higher among those who experienced a thrombo-embolic event compared with those who did not [30.1%/year ($n = 97$) vs. 3.5%/year ($n = 1175$)]. The majority of deaths occurred early after the thrombo-embolic event (*Figure 1*). The adjusted hazard ratio (HR) for death within 30 days after a thrombo-embolic event was 54.29 [95% confidence interval (CI) 41.35–71.28; $P < 0.001$]. After 30 days, the adjusted HR for death was 3.47 (95% CI 2.53–4.76; $P < 0.001$).

Patients who experienced thrombo-embolic events also had a higher risk of major bleeding with an event rate of 6.7%/year ($n = 10$) compared with 2.6%/year ($n = 779$) among those with no thrombo-embolic event. As shown in *Figure 2*, major bleeding occurred gradually. The adjusted HR for major bleeding within 30 days of a thrombo-embolic event was 10.37 (95% CI 3.87–27.8; $P < 0.001$); however, the increased hazard was no longer significant after 30 days (HR 1.73, 95% CI 0.77–3.88; $P = 0.183$).

A total of 22 (6.0%) patients had a recurrent stroke after a first thrombo-embolic event. The median (25th, 75th) time to recurrent stroke was 137 (30, 191) days; six strokes occurred within 30 days of the first thrombo-embolic event. The minimum time to recurrent stroke was 2 days, while maximum time was 505 days. The event rate for recurrent stroke after thrombo-embolic events was 7.1%/year, and 3 (13.6%) patients experienced a third stroke during follow-up.

Discussion

In ARISTOTLE, 365 patients had thrombo-embolic events during the course of the study. The majority of these events were strokes of ischaemic or unknown cause. Almost half of strokes resulted in no (23.2%) or minor (23.2%) neurological deficits; however, patients who experienced a first thrombo-embolic event were at substantially increased risk for death and recurrent stroke. There were only modest differences in the baseline characteristics of patients who did and did not experience thrombo-embolic events. The reduced dose of apixaban was used in a small percentage of patients who experienced

Table 2 Baseline characteristics

Characteristics	Overall (*n* = 18 201)	Thrombo-embolic event (*n* = 365)	No thrombo-embolic event (*n* = 17 836)	*P*-value
Age, median (25th, 75th) (years)	70.0 (63.0, 76.0)	71.0 (67.0, 77.0)	70.0 (63.0, 76.0)	<0.001
Female	6416 (35.3)	146 (40.0)	6270 (35.2)	0.057
Region				<0.001
North America	4474 (24.6)	82 (22.5)	4392 (24.6)	
Latin America	3468 (19.1)	67 (18.4)	3401 (19.1)	
Europe	7343 (40.3)	121 (33.2)	7222 (40.5)	
Asia Pacific	2916 (16.0)	95 (26.0)	2821 (15.8)	
Systolic BP, median (25th, 75th) (mmHg)	130.0 (120.0, 140.0)	130.0 (120.0, 140.5)	130.0 (120.0, 140.0)	
Weight, median (25th, 75th) (kg)	82.0 (70.0, 95.4)	76.5 (65.0, 90.8)	82.0 (70.0, 95.7)	<0.001
Prior MI	2585 (14.2)	67 (18.4)	2518 (14.1)	0.017
Prior clinically relevant or spontaneous bleeding	3040 (16.7)	64 (17.5)	2976 (16.7)	0.577
History of fall within previous year	753 (4.6)	21 (6.2)	732 (4.5)	0.118
Type of AF				0.003
Persistent or permanent	15 412 (84.7)	329 (90.1)	15 083 (84.6)	
Paroxysmal	2786 (15.3)	36 (9.9)	2750 (15.4)	
Prior use of VKAs (>30 days)	10 401 (57.1)	188 (51.5)	10 213 (57.3)	0.032
Renal function				<0.001
Normal (>80 mL/min)	7518 (41.5%)	116 (31.9%)	7402 (41.7%)	
Mild (>50–80 mL/min)	7587 (41.9%)	154 (42.3%)	7433 (41.9%)	
Moderate (>30–50 mL/min)	2747 (15.2%)	81 (22.3%)	2666 (15.0%)	
Severe (≤30 mL/min)	270 (1.5%)	13 (3.6%)	257 (1.4%)	
Qualifying risk factors				
Age ≥ 75 years	5678 (31.2%)	140 (38.4%)	5538 (31.0%)	0.001
Prior stroke, TIA, or SE	3538 (19.4%)	139 (38.1%)	3399 (19.1%)	<0.001
HF or reduced LVEF	6451 (35.4%)	141 (38.6%)	6310 (35.4%)	0.102
Diabetes	4547 (25.0%)	109 (29.9%)	4438 (24.9%)	0.018
Hypertension requiring treatment	15 916 (87.4%)	322 (88.2%)	15 594 (87.4%)	0.676
$CHADS_2$ score, mean (SD)	2.1 (1.1)	2.6 (1.2)	2.1 (1.1)	<0.001

AF, atrial fibrillation; BP, blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SD, standard deviation; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Table 3 Anticoagulant therapy before and after thrombo-embolic event (*n* = 365)

Anticoagulant	*n*	30 days before event[a]	7 days before event[b]	1 day before event[c]	3 days after event[d]	14 days after event[e]	30 days after event[f]
Study drug	365	319 (87.4)	271 (74.3)	248 (68.0)	177 (48.5)	200 (54.8)	211 (57.8)
Apixaban	175	152 (86.8)	130 (74.3)	117 (66.9)	85 (48.6)	96 (54.9)	102 (58.3)
Warfarin	190	167 (87.9)	141 (74.2)	131 (69.0)	92 (48.4)	104 (54.7)	109 (57.4)
VKA		6 (1.6)	6 (1.6)	4 (1.1)	15 (4.1)	18 (4.9)	19 (5.2)
Clopidogrel		15 (4.1)	15 (4.1)	15 (4.1)	28 (7.7)	29 (8.0)	30 (8.2)
Aspirin		100 (27.4)	93 (25.5)	89 (24.4)	119 (32.6)	126 (34.5)	129 (35.3)
Study drug + aspirin		80 (21.9)	65 (17.8)	59 (16.2)	52 (14.3)	62 (17.0)	65 (17.8)
Aspirin + clopidogrel		7 (1.9)	7 (1.9)	7 (1.9)	19 (5.2)	20 (5.5)	21 (5.8)

Rows not mutually exclusive.
VKA, vitamin K antagonist.
[a]On drug 30 days before event defined as receiving study drug at least once in the 30 days before event.
[b]On drug 7 days before event defined as receiving study drug at least once in the 7 days before event.
[c]On drug before event defined as receiving study drug the day before event.
[d]On drug 3 days after event defined as receiving study drug at least once in the 3 days following event.
[e]On drug 14 days after event defined as receiving study drug at least once in the 14 days following event.
[f]On drug 30 days after event defined as receiving study drug at least once in the 30 days following event.

Table 4 Study drug interruption and resumption in relation to the thrombo-embolic event

	Apixaban (*n* = 175)	Warfarin (*n* = 190)	Overall (*n* = 365)
Not on study drug[a]	58 (33.1)	59 (31.1)	117 (32.1)
On study drug[a]	117 (66.9)	131 (68.9)	248 (67.9)
No interruption[b]	50 (42.7)	51 (38.9)	101 (40.7)
Interruption[b]	67 (57.3)	80 (61.1)	147 (59.3)
Not resumed[c]	49 (73.1)	55 (68.8)	104 (70.7)
Resumed[c]	18 (26.9)	25 (31.2)	43 (29.3)
Days to resumption, median (25th, 75th)	12 (6, 30)	13 (7, 30)	13 (7, 30)

Data presented as *n* (%), unless otherwise indicated.
[a]On study drug defined as receiving study drug the day before event.
[b]Interruption is defined as not receiving study drug on day of event or at least one of 3 days after event.
[c]Resumed is defined as receiving study drug on at least one day following interruption.

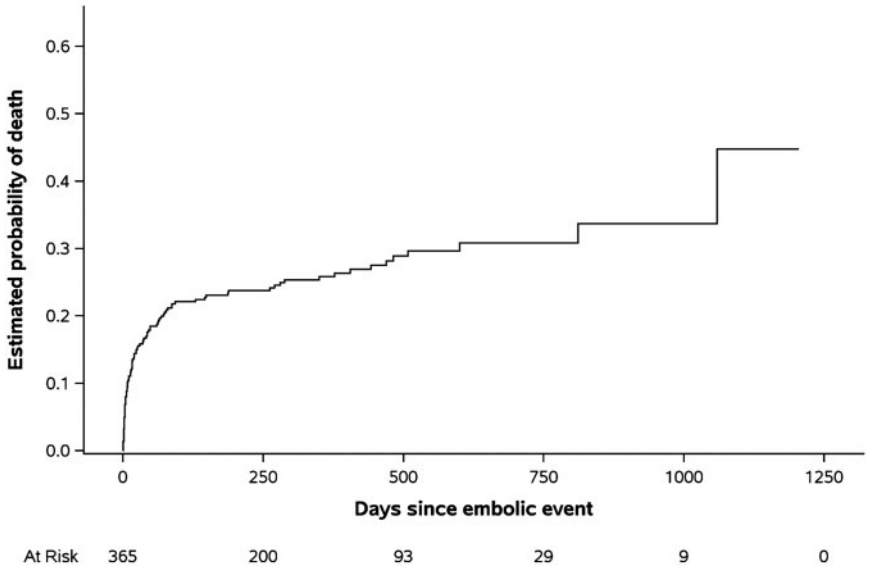

Figure 1 The Kaplan–Meier plot of estimated probability of death after a thrombo-embolic event.

embolic events. Anticoagulant use immediately prior to thrombo-embolic events was low, which may have been a potential cause of the thrombo-event. Limited use of anticoagulation may have contributed to the high mortality and recurrence of stroke after thrombo-embolic events.

A previous analysis from ARISTOTLE demonstrated a high risk of mortality, myocardial infarction, and stroke after major bleeding events.[14] It is likely that patients at high risk of thrombo-embolic events share many of the same characteristics as those at high risk for bleeding.[15] However, risk stratification strategies for patients with AF and either bleeding or thrombo-embolic events on anticoagulant therapy have not yet been established. Our results demonstrating the short-term increased risk after thrombo-embolic events may reflect the presence of the same initiator for both bleeding and thrombo-embolic events. The use of anticoagulant therapy, including study drug, decreased after thrombo-embolic events. One potential explanation is the increased use of less effective antiplatelet therapies after an initial thrombo-embolic event.

The clinical consequences of thrombo-embolic events in ARISTOTLE, which were mostly stroke of ischaemic/unknown cause, were not as severe as those reported in other AF populations.[13] Approximately half of those in our study who experienced a stroke had relatively mild neurological deficits and more than half had a Rankin score ≤2. As previously published, neurological deficits in AF-related stroke become less severe when patients are adequately anticoagulated before the onset of stroke.[16] It is important to note that the risk of recurrent stroke and mortality were high even though neurological deficits after the initial stroke in ARISTOTLE were relatively mild.

One interesting finding of this subgroup analysis is that more than 30% of thrombo-embolic events (117 out of 365) occurred in patients

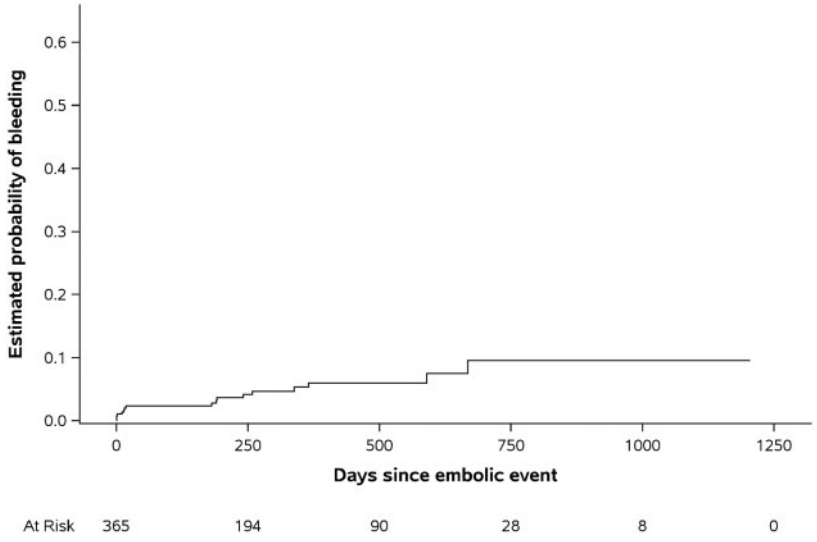

Figure 2 The Kaplan–Meier plot of estimated probability of major bleeding after a thrombo-embolic event.

who did not receive study drug one day before the thrombo-embolic event, even though all patients were in a study comparing apixaban and dose-adjusted warfarin. Study drug use decreased from 30 days before the thrombo-embolic event to the date of the event. Despite strong recommendations encouraging the use of anticoagulants in patients with AF at risk of stroke, adherence to anticoagulant therapy in clinical practice is still low.[6,17] In many instances, there is no clear reason as to why patients stop anticoagulant therapy.[10,17] Our results suggest a relationship between not taking study drug and the onset of thrombo-embolic events and subsequent high mortality. Reasons for stopping study drug included bleeding and other adverse events in roughly one-third of patients. One-fifth discontinued study drug due to emergency or elective procedures, and half discontinued study drug due to patient request, physician choice, or other unspecified reasons. Clinical outcomes in patients with AF might be improved by avoiding the potentially unnecessary discontinuation of anticoagulant agents. There were no major differences between the baseline characteristics of patients who did and did not experience thrombo-embolic events in this study, which suggests that there may be other important factors that contribute to thrombo-embolic events in patients with AF on anticoagulant therapy. The impact of not taking anticoagulant therapy in patients with AF is an important issue that should be addressed in future studies.[6,18]

Another interesting finding is that 147 of 248 patients on study drug interrupted study drug on the day of the thrombo-embolic event or on at least 1 of 3 days after the event. A total of 43 (29.3%) patients resumed study drug a median of 13 days after interruption, suggesting that physicians tended to stop anticoagulant therapy in patients who experienced a thrombo-embolic event. Of note, more than 30% of patients who experienced a thrombo-embolic event received parenteral anticoagulant therapy during the trial. Though recently published practice guidelines do not recommend the use of parenteral anticoagulants after stroke due to an increased risk of bleeding, including intracranial bleeding,[19] it is likely that a substantial number of patients received parenteral anticoagulants as bridging therapy. Timing of their use was not recorded in ARISTOTLE; therefore, the impact of the use of parenteral anticoagulant therapy cannot be assessed within this study. Despite recently published practice guidelines that recommend starting oral anticoagulant therapy 1–12 days after stroke, depending on the clinical profile,[5] some physicians in ARISTOTLE chose to use antithrombotic treatment, including parenteral anticoagulants, aspirin, and clopidogrel, after thrombo-embolic events. One possible explanation for this is that the ARISTOTLE study protocol did not include specific guidance about the management of patients who experienced a thrombo-embolic event other than to restart oral anticoagulant therapy when clinically appropriate.

Patients who experienced thrombo-embolic events during the study were at a higher risk for death and recurrent stroke as compared with those who did not. Of the 365 patients who experienced a thrombo-embolic event, 97 died during the course of the trial. The high mortality risk persisted even after excluding events that occurred within 30 days after thrombo-embolic events. The higher risk of mortality and recurrent stroke seen in our study might be explained by the decreased use and low resumption rates of oral anticoagulattherapy after thrombo-embolic events.

Our study has several limitations. One major limitation is the small number of patients who experienced thrombo-embolic events. Another important limitation is that our analysis was a post-hoc analysis comparing patients who did and did not experience thrombo-embolic events during the ARISTOTLE study and was not a prespecified subanalysis. The criteria used to define thrombo-embolic events were based on the predefined primary efficacy endpoint of the ARISTOTLE trial; however, we excluded haemorrhagic stroke. We have included all available data; however, some data, such as the use of parenteral anticoagulant and fibrinolysis, might be incomplete. Despite these limitations, our main finding of higher mortality and stroke recurrence and increased bleeding within 30 days after

thrombo-embolic events is not influenced by the definition of thrombo-embolic events.

In anticoagulated patients with AF, thrombo-embolic events are rare but associated with high short- and long-term morbidity and mortality. Substantial numbers of patients are not receiving oral anticoagulattherapy before and, despite this risk, after a first thrombo-embolic event.

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