Characteristics and Outcomes of Atrial Fibrillation in Patients With Thyroid Disease (from the ARISTOTLE Trial)

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Abstract

Whether patients with atrial fibrillation (AF) and thyroid disease are clinically distinct from those with AF and no thyroid disease is unknown. Furthermore, the effectiveness of anticoagulation for prevention of AF-related thromboembolic events in patients with thyroid disease has not been adequately studied. Patients enrolled in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, which compared apixaban with warfarin in patients with AF (n = 18,201), were categorized by thyroid disease history at randomization (hypothyroidism, hyperthyroidism, and no thyroid disease). Adjusted hazard ratios derived from Cox models were used to compare outcomes by thyroid disease history. Associations between randomized treatment and outcomes by thyroid disease history were examined using Cox models with interaction terms. A total of 18,021/18,201 (99%) patients had available thyroid disease history at randomization: 1,656 (9%) had hypothyroidism, 321 (2%) had hyperthyroidism, and 16,044 (89%) had no thyroid disease. When compared with those without a history of thyroid disease, patients with hypo- or hyperthyroidism were more likely to be female (60.4% vs 32.1%; 52.0% vs 32.1%; both p <0.0001). Patients with hypothyroidism were older (73 vs 70 years, p <0.0001) and more likely to have had previous falls (8.7% vs 4.3%, p <0.0001). There was no difference in clinical outcomes by thyroid disease history. The benefit of apixaban compared with warfarin was similar regardless of thyroid disease history (interaction p >0.10). In conclusion, despite differences in baseline characteristics of patients with and without thyroid disease, their clinical outcomes were similar. The benefit of apixban compared with warfarin was preserved regardless of thyroid disease history.

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Atrial fibrillation (AF) is associated with an increased risk of cerebrovascular events and systemic embolism.[1] The risk of embolic events associated with AF can be significantly reduced with oral anticoagulation, and randomized controlled trials have confirmed the efficacy and safety of nonvitamin K antagonist oral anticoagulants compared with warfarin. [2–6] A close relation exists between AF and thyroid disease. Hyperthyroidism is strongly associated with the development of AF.[7,8] Although hypothyroidism does not portend an increased risk of AF, there is considerable overlap between these conditions due to common risk factors.[9] Thyroid function influences the hemostatic system, with response to systemic anticoagulation being unpredictable.[10–13] Despite the known effects of thyroid disease on the development and treatment of AF, there remains a paucity of data describing the characteristics, outcomes and response to therapy of patients with AF and thyroid disease. In this secondary analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), we compared clinical characteristics of patients with AF with and without thyroid disease; evaluated clinical outcomes according to thyroid disease history; and analyzed the treatment effect of apixaban compared with warfarin according to thyroid disease history.

Methods

Data for this analysis were obtained from the ARISTOTLE trial. The design and results of this trial have been previously published.[2,14] Briefly, ARISTOTLE was a multinational, randomized, double-blind, controlled trial that evaluated whether apixaban, a direct factor Xa inhibitor, was non-inferior to warfarin for the prevention of stroke or systemic embolism in patients with AF enrolled 18,201 patients with AF or atrial flutter and at least 1 additional risk factor for stroke. If noninferiority of apixaban to warfarin was established, the trial was designed to examine superiority of apixaban over warfarin. Patients with moderate or severe mitral stenosis, prosthetic mechanical heart valves, AF due to a reversible cause, previous intracranial hemorrhage, severe renal insufficiency, stroke within 7 days before randomization, or need for aspirin at a dose of >165 mg per day or dual antiplatelet therapy were excluded. Patients were randomized to receive either dose-adjusted warfarin (target international normalized ratio (2.0 to 3.0) or apixaban (5 mg twice daily). Apixaban dosing was reduced to 2.5 mg twice daily in patients with 2 or more of the following criteria: age 80 years, weight 60 kg, or creatinine level 1.5 mg/dl. Median follow-up was 1.8 years. Ethics committees at all participating sites approved the protocol and all patients provided written informed consent.

Of the 18,201 patients enrolled in ARISTOTLE, we identified 18,021 with available thyroid disease history (hypothyroidism, hyperthyroidism, or no thyroid disease) at the time of randomization; 43 patients were excluded due to unavailable thyroid history, and 137 patients with thyroid disease were excluded due to unavailable thyroid disease type.

The classification of thyroid disease history (hypo- vs hyper- vs no disease) was determined based on investigator responses on the ARISTOTLE data intake form. Patients in whom the presence or type of thyroid disease was not available, but who were noted to be taking thyroid replacement hormone or antithyroid therapy were included as hypo- and hyperthyroid, respectively. Patients who were designated as having hyperthyroidism but

were documented to be taking thyroid replacement hormone were categorized as being hypothyroid.

The primary outcome of this analysis was a combined end point of stroke (ischemic or hemorrhagic) or systemic embolism. The primary safety outcome was major bleeding, according to the criteria defined by the International Society on Thrombosis and Haemostasis. Secondary outcomes included any stroke, ischemic stroke (including unknown type of stroke), hemorrhagic stroke, all-cause death, myocardial infarction, hospitalization for heart failure, and any bleeding event.

Patients were grouped by categories of thyroid disease history (hypothyroidism, hyperthyroidism, and no thyroid disease) for all analyses. In each analysis, patients with hypothyroidism were compared with patients with no thyroid disease; patients with hyperthyroidism were compared with patients with no thyroid disease. Baseline characteristics of the 3 groups were summarized as medians (twenty-fifth and seventy-fifth percentiles) for continuous variables and as percentages (frequencies) for categorical variables. Continuous and categorical variables were compared across the 3 groups using the Kruskal-Wallis and chi-square tests. Pairwise comparisons between hypo- and hyperthyroidism and the no thyroid disease group were performed using the Wilcoxon and chi-square tests. Given the exploratory nature of these comparisons, corrections for multiplicity were not applied. Unadjusted and adjusted hazard ratios (HRs) comparing the hypothyroidism and hyperthyroidism groups with the no thyroid disease group were derived using Cox models. Variables for adjusted results were selected from previously developed models. Adjusted HRs derived from Cox models were used to compare outcomes of interest by thyroid disease category. Pairwise comparisons between each thyroid disease history group and the no thyroid disease history group were adjusted for multiplicity using simulations. Associations between randomized treatment (apixaban vs warfarin) and outcomes, stratified by thyroid disease history, were examined using a Cox model with interaction terms. All analyses were performed using SAS v9.4 TS1M4 (SAS, Inc., Cary, North Carolina).

Results

Of the 18,021 patients who met the inclusion criteria and had available thyroid disease history at randomization, 1,656 (9%) had a history of hypothyroidism, 321 (2%) had a history of hyperthyroidism, and 16,044 (89%) as had no history of thyroid disease. Baseline characteristics of the study population are shown in Table 1.

Table 2 shows the association between types of thyroid disease and the end points of interest, expressed as unadjusted and adjusted HRs. Covariates included in the adjusted models are provided as a footnote to Table 2. Clinical outcomes of patients with hypo- or hyperthyroidism were similar to those with no thyroid disease, including stroke/systemic embolism (adjusted HR 0.76, 95% confidence interval [CI] 0.51 to 1.14, p = 0.24; adjusted HR 0.59, 95% CI 0.21 to 1.60, p = 0.41), all-cause death (adjusted HR 0.91, 95% CI 0.72 to 1.14, p = 0.57; adjusted HR 0.95, 95% CI 0.57 to 1.61, p = 0.97), and major bleeding

(adjusted HR 1.00, 95% CI 0.76 to 1.31, p = 1.00; adjusted HR 0.81, 95% CI 0.41 to 1.60, p = 0.73).

Figure 1 shows the associations between randomized treatments (apixaban vs warfarin) and end points, stratified by thyroid disease history. Interaction tests between randomized treatment and thyroid disease history were >0.10 for the primary outcome, primary safety end point, and all secondary outcomes including stroke/systemic embolism (interaction p value = 0.44), all-cause death (interaction p value = 0.42), and major bleeding (interaction p value = 0.67). These results demonstrate that apixaban was superior to warfarin in patients with and without thyroid disease, a finding that is consistent with the overall results of the ARISTOTLE trial.

Discussion

The relation between thyroid disease and AF has been well described. The risk of AF is proportional to circulating levels of free thyroxine and inversely proportional to thyroid stimulating hormone level, with an increase in risk of AF present even in patients with subclinical hyperthyroidism.[15] Furthermore, new onset AF in patients without a history of thyroid disease is an independent predictor of subsequent development of hyperthyroidism. [16] Hypothyroidism is not associated with an increased risk of AF, but considerable overlap exists between these conditions given their high prevalence and similar risk factors.[9]

In general, hyperthyroidism is considered a prothrombotic condition whereas hypothyroidism may lead to a hypocoagulable state with an increased risk of bleeding.[17,18] Additionally, thyroid dysfunction may affect response to oral anticoagulation, potentially making prevention of AF-related thrombotic events without the development of bleeding complications difficult.[12,13,17] Despite this, there is a paucity of literature describing patients with both diagnoses. Furthermore, whether it is safe and effective to treat patients with AF and thyroid disease with traditional anticoagulation strategies is unknown. The current analysis addresses these issues through the following notable findings. Baseline characteristics of patients with AF and a history of thyroid disease differ significantly from those with AF without a history of thyroid disease. When compared with patients without a history of thyroid disease, those with AF and a history of thyroid disease have similar rates of stroke/systemic embolism, all-cause death, and major bleeding in the setting of oral anticoagulation. Finally, apixaban is superior to warfarin in patients with and without a history of thyroid disease for all investigated efficacy and safety end points.

We demonstrated differences in the baseline characteristics of patients with AF and a history of thyroid disease compared with those without thyroid disease. Patients with any thyroid disease history were more likely to live in North America, likely representing ascertainment bias associated with more frequent testing in this region. Additionally, patients with a history of thyroid disease were more likely to have previous use of a vitamin K antagonist for >30 days and have previous clinically relevant or spontaneous bleeding, possibly related to the effect of thyroid disease on the coagulation system. Finally, patients with a history of hyperthyroidism were less commonly taking amiodarone at the time of enrollment, likely due to concern that amiodarone use had caused or might exacerbate underlying

hyperthyroidism and the potential development of thyroid storm. Interestingly, despite a known association between worsening of hypothyroidism and amiodarone use, use of this medication was similar in those with a history of hypothyroidism compared with those without a history of thyroid disease. This may be attributed to the fact that management of new or existing hypothyroidism in the amiodarone-treated patient is far less challenging than drug-induced hyperthyroidism.

Because hypo- and hyperthyroidism are believed to alter the coagulation system and potentially affect responses to oral anticoagulation, it has been hypothesized that thyroid disease may affect the efficacy and safety of AF-related stroke prevention. Furthermore, older age and increased falls seen in patients with hypothyroidism in our analysis may also increase the risk of bleeding complications. Despite this, our analysis showed that, with regard to the evaluated efficacy and safety end points, patients with AF and either hypo- or hyperthyroidism treated with oral anticoagulation had similar clinical outcomes compared with those without thyroid disease. Additionally, the finding in the larger ARISTOTLE trial that apixaban was superior to warfarin was preserved in this subgroup analysis, irrespective of thyroid disease history. Our findings suggest that patients with AF and thyroid disease should be managed with oral anticoagulation similarly to patients with AF and no thyroid disease.

To our knowledge, this is the first study examining differences in patient characteristics, clinical outcomes, and anticoagulation strategy in patients with AF and thyroid disease. Current American College of Cardiology/American Heart Association guidelines have few recommendations regarding the management of AF in patients with thyroid disease, and do not address anticoagulation strategies in this patient group.[8] This novel analysis provides important insight regarding patients with AF and thyroid disease that can be used to further our understanding of how to clinically manage this important patient population. Given the significant differences in patient characteristics identified, however, future prospective and randomized trials should be aimed at validating and expanding upon these results.

Because this analysis was limited to patients enrolled in a clinical trial, the results may not be generalizable to all patients with AF and thyroid disease. Although we adjusted for baseline differences using multivariable analyses, patients were not randomized based on baseline thyroid disease history and thus our results represent associations as opposed to causal relations. Inherent to a secondary analysis is that some important information may not have been collected in the original trial and therefore was not available for our analysis. Specifically, we were only able to analyze patients based on baseline thyroid disease history at the time of study entry; details regarding changes in thyroid disease history and treatment during the study period were not available. Also, classification of thyroid disease may not have been accurate. Patients who were initially diagnosed with hypothyroidism could have developed hyperthyroidism due to over-supplementation. Likewise, some patients may have initially been diagnosed with hyperthyroidism and developed hypothyroidism as a result of therapy. Finally, patients with a history of thyroid disease who were adequately treated may have been functionally euthyroid while enrolled in the study. Thyroid hormone levels were not available to confirm the accuracy of the reported diagnosis. An analysis using hormone levels and specific thyroid treatments could yield different results. Finally, because only

patients without a reversible cause of AF were included in ARISTOTLE, our study included a comparatively small number of patients with hyperthyroidism compared with hypothyroidism. Patients with hyperthyroidism who were included likely had very well controlled disease. Thus, our results are likely not generalizable to patients with clinically important hyperthyroidism.

In conclusion, significant differences exist between patients with AF and thyroid disease history compared with those without thyroid disease history. Despite these differences, AF-related clinical outcomes and anticoagulation treatment response were similar irrespective of thyroid disease history. These results suggest that patients with AF and thyroid disease should be treated with oral anticoagulation similarly to those with AF and no thyroid disease.

Acknowledgments

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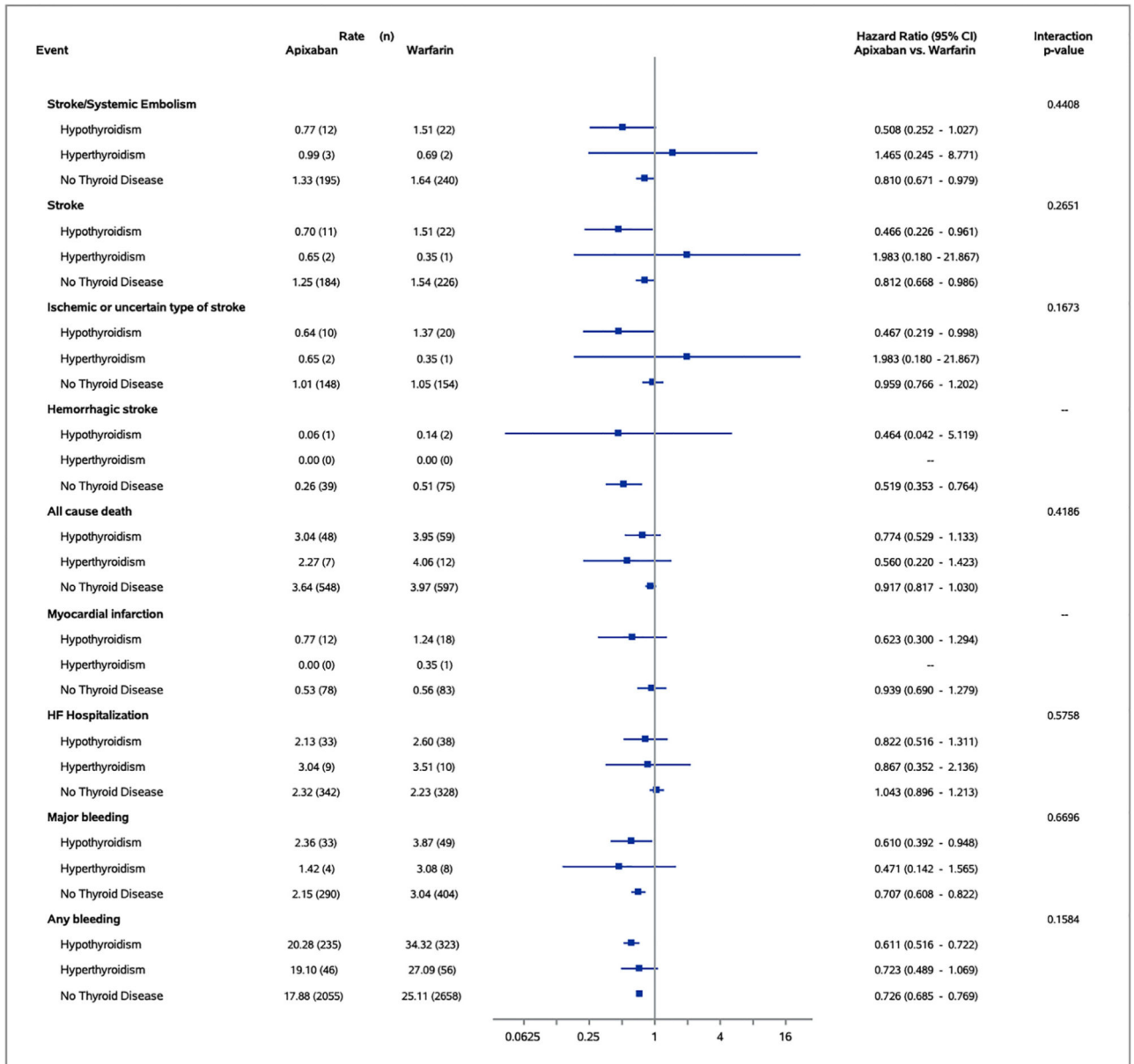| Event	Rate (n) Apixaban	Warfarin		Hazard Ratio (95% CI) Apixaban vs. Warfarin	Interaction p-value
Stroke/Systemic Embolism					0.4408
Hypothyroidism	0.77 (12)	1.51 (22)		0.508 (0.252 - 1.027)	
Hyperthyroidism	0.99 (3)	0.69 (2)		1.465 (0.245 - 8.771)	
No Thyroid Disease	1.33 (195)	1.64 (240)		0.810 (0.671 - 0.979)	
Stroke					0.2651
Hypothyroidism	0.70 (11)	1.51 (22)		0.466 (0.226 - 0.961)	
Hyperthyroidism	0.65 (2)	0.35 (1)		1.983 (0.180 - 21.867)	
No Thyroid Disease	1.25 (184)	1.54 (226)		0.812 (0.668 - 0.986)	
Ischemic or uncertain type of stroke					0.1673
Hypothyroidism	0.64 (10)	1.37 (20)		0.467 (0.219 - 0.998)	
Hyperthyroidism	0.65 (2)	0.35 (1)		1.983 (0.180 - 21.867)	
No Thyroid Disease	1.01 (148)	1.05 (154)		0.959 (0.766 - 1.202)	
Hemorrhagic stroke					--
Hypothyroidism	0.06 (1)	0.14 (2)		0.464 (0.042 - 5.119)	
Hyperthyroidism	0.00 (0)	0.00 (0)		--	
No Thyroid Disease	0.26 (39)	0.51 (75)		0.519 (0.353 - 0.764)	
All cause death					0.4186
Hypothyroidism	3.04 (48)	3.95 (59)		0.774 (0.529 - 1.133)	
Hyperthyroidism	2.27 (7)	4.06 (12)		0.560 (0.220 - 1.423)	
No Thyroid Disease	3.64 (548)	3.97 (597)		0.917 (0.817 - 1.030)	
Myocardial infarction					--
Hypothyroidism	0.77 (12)	1.24 (18)		0.623 (0.300 - 1.294)	
Hyperthyroidism	0.00 (0)	0.35 (1)		--	
No Thyroid Disease	0.53 (78)	0.56 (83)		0.939 (0.690 - 1.279)	
HF Hospitalization					0.5758
Hypothyroidism	2.13 (33)	2.60 (38)		0.822 (0.516 - 1.311)	
Hyperthyroidism	3.04 (9)	3.51 (10)		0.867 (0.352 - 2.136)	
No Thyroid Disease	2.32 (342)	2.23 (328)		1.043 (0.896 - 1.213)	
Major bleeding					0.6696
Hypothyroidism	2.36 (33)	3.87 (49)		0.610 (0.392 - 0.948)	
Hyperthyroidism	1.42 (4)	3.08 (8)		0.471 (0.142 - 1.565)	
No Thyroid Disease	2.15 (290)	3.04 (404)		0.707 (0.608 - 0.822)	
Any bleeding					0.1584
Hypothyroidism	20.28 (235)	34.32 (323)		0.611 (0.516 - 0.722)	
Hyperthyroidism	19.10 (46)	27.09 (56)		0.723 (0.489 - 1.069)	
No Thyroid Disease	17.88 (2055)	25.11 (2658)		0.726 (0.685 - 0.769)	

0.0625 0.25 1 4 16

Figure 1.
Association between randomized treatments and end points by thyroid disease status.

Table 1

Baseline characteristics by history of thyroid disease status

Characteristic	History of thyroid disease			p value[*]		
	Hypothyroidism (n = 1,656)	Hyperthyroidism (n = 321)	No Disease (n = 16,044)	Hypo vs No	Hyper vs No	Overall
Age, median (25th, 75th) (years)	73 (66, 79)	69 (62, 76)	70 (62, 76)	<0.0001	0.8382	<0.0001
Women	1001 (60.4%)	167 (52.0%)	5145 (32.1%)	<.0001	<.0001	<0.0001
Region of enrollment				<0.0001	<.0001	<0.0001
North America	695 (42.0%)	56 (17.4%)	3710 (23.1%)			
Latin America	290 (17.5%)	36 (11.2%)	3131 (19.5%)			
Europe	544 (32.9%)	177 (55.1%)	6477 (40.4%)			
Asia	127 (7.7%)	52 (16.2%)	2726 (17.0%)			
Systolic BP, median (25th, 75th) (mm Hg)	130 (120, 140)	130 (120, 140)	130 (120, 140)	0.0028	0.4882	0.0099
Weight, median (25th, 75th) (kilograms)	80 (69, 95)	78 (66, 90)	82 (70, 96)	0.0526	<.0001	<0.0001
Prior Myocardial Infarction	235 (14.2%)	46 (14.3%)	2276 (14.2%)	0.9884	0.9451	0.9976
Prior stroke, transient ischemic attack, or systemic embolism	319 (19.3%)	74 (23.1%)	3110 (19.4%)	0.9056	0.1002	0.2540
Heart failure or reduced left ventricular ejection fraction	478 (28.9%)	108 (33.6%)	5764 (35.9%)	<.0001	0.3988	<0.0001
Hypertension requiring treatment	1472 (88.9%)	289 (90.0%)	13981 (87.1%)	0.0420	0.1250	0.0435
Prior clinically relevant or spontaneous bleeding	378 (22.8%)	66 (20.6%)	2582 (16.1%)	<.0001	0.0315	<0.0001
History of fall within previous year	132 (8.7%)	13 (4.3%)	601 (4.1%)	<.0001	0.8573	<0.0001
Diabetes Mellitus	473 (28.6%)	81 (25.2%)	3956 (24.7%)	0.0005	0.8125	0.0022
End-organ damage	96 (5.8%)	18 (5.6%)	650 (4.1%)	0.0007	0.1644	0.0017
Type of Atrial fibrillation				<.0001	0.0140	<0.0001
Paroxysmal	312 (18.8%)	63 (19.6%)	2359 (14.7%)			
Persistent or permanent	1344 (81.2%)	258 (80.4%)	13682 (85.3%)			
Atrial fibrillation/Flutter	1333 (81.1%)	256 (80.3%)	13670 (85.7%)	<.0001	0.0066	<0.0001
Heart rate in atrial fibrillation/Flutter, median (25th, 75th) (beats per minute)	77 (67, 90)	80 (68, 92)	79 (69, 90)	0.0005	0.7391	0.0020
Sinus rhythm	262 (15.9%)	56 (17.6%)	2043 (12.8%)	0.0003	0.0121	0.0001
HR in sinus rhythm, median (25th, 75th) (beats per minute)	61 (55, 67)	64 (56, 71)	62 (56, 70)	0.0542	0.7259	0.1391
Prior vitamin K antagonist use for >30 days	1101 (66.5%)	241 (75.1%)	8978 (56.0%)	<0.0001	<0.0001	<0.0001
CHADS$_2$ score, mean (standard deviation)	2.21 (1.12)	2.20 (1.17)	2.11 (1.10)	0.0002	0.2773	0.0005

Characteristic	History of thyroid disease			p value*		
	Hypothyroidism (n = 1,656)	Hyperthyroidism (n = 321)	No Disease (n = 16,044)	Hypo vs No	Hyper vs No	Overall
CHADS₂ score				0.0005	0.6900	0.0033
1	493 (29.8%)	108 (33.6%)	5532 (34.5%)			
2	622 (37.6%)	110 (34.3%)	5718 (35.6%)			
3	541 (32.7%)	103 (32.1%)	4794 (29.9%)			
Medications at randomization						
ACE inhibitor or angiotensin receptor blocker	1116 (67.8%)	235 (74.4%)	11331 (71.9%)	0.0005	0.3263	0.0013
Amiodarone	185 (11.2%)	18 (5.7%)	1824 (11.6%)	0.6915	0.0012	0.0050
Beta-blocker	1067 (64.8%)	226 (71.5%)	10076 (63.9%)	0.4583	0.0052	0.0166
Aspirin	447 (27.0%)	86 (26.8%)	5048 (31.5%)	0.0002	0.0741	0.0002
Clopidogrel	41 (2.5%)	7 (2.2%)	289 (1.8%)	0.0533	0.6135	0.1427
Digoxin	483 (29.3%)	106 (33.5%)	5189 (32.9%)	0.0033	0.8118	0.0126
Any calcium channel blocker	573 (34.8%)	107 (33.9%)	4842 (30.7%)	0.0006	0.2292	0.0017
Statin	808 (49.1%)	141 (44.6%)	6481 (41.1%)	<0.0001	0.2083	<0.0001
Nonsteroidal anti-inflammatory agent	206 (12.5%)	31 (9.8%)	1278 (8.1%)	<0.0001	0.2724	<0.0001
Gastric antacid drugs	430 (26.1%)	80 (25.3%)	2828 (17.9%)	<0.0001	0.0007	<0.0001
Antithyroid preparations	2 (0.1%)	71 (22.1%)	0 (0.0%)			
Thyroid preparations	1200 (72.5%)	0 (0.0%)	0 (0.0%)			
Iodine preparations	7 (0.4%)	0 (0.0%)	1 (0.0%)			
Any thyroid therapy	1202 (72.6%)	71 (22.1%)	1 (0.0%)			
Renal function				<0001	0.3563	<0.0001
Normal (80 ml/min)	535 (32.3%)	129 (40.2%)	6765 (42.2%)			
Mild impairment (>50–80 ml/min)	710 (42.9%)	140 (43.6%)	6667 (41.6%)			
Moderate impairment (>30–50 ml/min)	356 (21.5%)	47 (14.6%)	2326 (14.5%)			
Severe impairment (30 ml/min)	48 (2.9%)	1 (0.3%)	220 (1.4%)			

*
Exploratory.Data presented as no. (%), unless otherwise indicated.ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BP = blood pressure; bpm = beats per minute; HF = heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SD = standard deviation; SE = systemic embolism; TIA = transient ischemic attack; VKA = vitamin K antagonist.

Table 2

Association between types of thyroid disease and end points

| End point | Hypothyroidism | | | | | Hyperthyroidism | | | | | No thyroid disease | Overall p value | |
| | Unadjusted | | | Adjusted[‡] | | Unadjusted | | | Adjusted[‡] | | | Unadjusted | Adjusted[‡] |
	Rate (events)	hazard ratio* (95% confidence Interval)	p value	hazard ratio* (95% confidence Interval)	p value	Rate (events)	hazard ratio* (95% confidence Interval)	p value	hazard ratio* (95% confidence Interval)	p value	Rate (events)		
Stroke/systemic embolism	1.13 (34)	0.76 (0.51–1.13)	0.23	0.76 (0.51–1.14)	0.24	0.84 (5)	0.57 (0.21–1.55)	0.38	0.59 (0.21–1.60)	0.41	1.48 (435)	0.14	0.16
Any stroke	1.09 (33)	0.78 (0.53–1.16)	0.31	0.79 (0.53–1.20)	0.36	0.50 (3)	0.36 (0.10–1.308)	0.15	0.38 (0.10–1.38)	0.17	1.40 (410)	0.09	0.11
Ischemic stroke[†]	0.99 (30)	0.96 (0.63–1.47)	0.98	0.96 (0.62–1.48)	0.97	0.50 (3)	0.49 (0.14–1.78)	0.39	0.50 (0.14–1.83)	0.40	1.03 (302)	0.47	0.48
Hemorrhagic stroke	0.10 (3)	0.26 (0.07–0.94)	0.04	0.30 (0.08–1.11)	0.08	0.00 (0)	–	–	–	–	0.38 (114)	0.07	0.12
All-cause death	3.48 (107)	0.92 (0.73–1.15)	0.61	0.91 (0.72–1.14)	0.57	3.15 (19)	0.83 (0.49–1.39)	0.65	0.95 (0.57–1.61)	0.97	3.81 (1145)	0.50	0.63
Myocardial infarction	0.99 (30)	1.82 (1.17–2.83)	0.01	1.43 (0.90–2.26)	0.16	0.17 (1)	0.31 (0.03–2.88)	0.42	0.33 (0.04–3.15)	0.47	0.54 (161)	0.01	0.11
Heart failure hospitalization	2.36 (71)	1.03 (0.78–1.36)	0.96	0.99 (0.74–1.31)	0.99	3.27 (19)	1.44 (0.86–2.42)	0.22	1.45 (0.85–2.46)	0.23	2.28 (670)	0.29	0.30
International Society on Thrombosis and Haemostasis major bleeding	3.08 (82)	1.19 (0.91–1.54)	0.27	1.00 (0.76–1.31)	1.00	2.22 (12)	0.86 (0.45–1.64)	0.84	0.81 (0.41–1.60)	0.73	2.59 (694)	0.29	0.79
Any bleeding	26.58 (558)	1.22 (1.11–1.35)	<.0001	1.07 (0.96–1.19)	0.29	22.79 (102)	1.07 (0.86–1.34)	0.75	1.05 (0.83–1.32)	0.88	21.35 (4713)	<.0001	0.34

*
Hazard ratios *vs* no thyroid disease.

[†]
Includes unknown type of stroke.Pairwise p values and 95% confidence intervals corrected by multiplicity

[‡]
Covariates included in adjusted models by outcome: Any Stroke and Ischemic Stroke: Adjusted by region, diabetes, hypertension, moderate or severe valvular heart disease, prior stroke, transient ischemic attack or systemic embolism, prior use of vitamin K antagonist >30 days, congestive heart failure, age, and weight (nonlinear).Hemorrhagic Stroke: Adjusted by sex, region, coronary artery disease, prior myocardial infarction, history of bleeding, anemia, CHADS2 score, renal disease, and age.All-cause death: Adjusted by sex, region, hypertension, moderate or severe valvular heart disease, prior myocardial infarction, prior stroke, transient ischemic attack or systemic embolism, anemia, current smoker, prior use of vitamin K antagonist >30 days, New York Heart Association class, CHADS2 score, renal disease, congestive heart failure, age (nonlinear), systolic blood pressure (nonlinear), diastolic blood pressure (nonlinear), and weight.Myocardial Infarction: Adjusted by region, diabetes, coronary artery disease, prior myocardial infarction, New York Heart Association class, renal disease, congestive heart failure, and age (nonlinear).Heart failure hospitalization:

Adjusted by diabetes, moderate or severe valvular heart disease, prior myocardial, renal disease, left bundle branch block, current smoker, New York Heart Association class, congestive heart disease, age (nonlinear), systolic blood pressure (nonlinear), and weight (nonlinear).