

# Dyslipidemia and Risk of Cardiovascular Events in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Therapy: Insights From the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) Trial

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**Background**—Dyslipidemia is a major risk factor for cardiovascular events. The prognostic importance of lipoproteins in patients with atrial fibrillation is not well understood. We aimed to explore the association between apolipoprotein A1 (ApoA1) and B (ApoB) and cardiovascular events in patients with atrial fibrillation receiving oral anticoagulation.

**Methods and Results**—Using data from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, ApoA1 and ApoB plasma levels were measured at baseline in 14 884 atrial fibrillation patients. Median length of follow-up was 1.9 years. Relationships between continuous levels of ApoA1 and ApoB and clinical outcomes were evaluated using Cox models adjusted for cardiovascular risk factors, medication including statins, and cardiovascular biomarkers. A composite ischemic outcome (ischemic stroke, systemic embolism, myocardial infarction, and cardiovascular death) was used as the primary end point. Median (25th, 75th) ApoA1 and ApoB levels were 1.10 (0.93, 1.30) and 0.70 g/L (0.55, 0.85), respectively. In adjusted analyses, higher levels of ApoA1 were independently associated with a lower risk of the composite ischemic outcome (hazard ratio, 0.81;  $P < 0.0001$ ). Similar results were observed for the individual components of the composite outcome. ApoB was not significantly associated with the composite ischemic outcome ( $P = 0.8240$ ). Neither apolipoprotein was significantly associated with major bleeding. There was no interaction between lipoproteins and randomized treatment for the primary outcome (both  $P$  values  $\geq 0.2448$ ).

**Conclusions**—In patients with atrial fibrillation on oral anticoagulation, higher levels of ApoA1 were independently associated with lower risk of ischemic cardiovascular outcomes. Investigating therapies targeting dyslipidemia may thus be useful to improve cardiovascular outcomes in patients with atrial fibrillation.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00412984. (*J Am Heart Assoc.* 2018;7:e007444. DOI: 10.1161/JAHA.117.007444.)

**Key Words:** atrial fibrillation • biomarkers • cardiovascular disease • cerebrovascular disease/stroke

Atrial fibrillation (AF) is associated with an increased risk of stroke, mortality, and health costs worldwide.<sup>1,2</sup> Biomarkers have shown increasing promise in improving risk

prediction in AF.<sup>3,4</sup> Elevated levels of natriuretic peptides and troponins, signifying myocardial damage and stress, have each shown to more than double the risk of stroke and all-

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## Clinical Perspective

### What Is New?

- In patients with atrial fibrillation treated with oral anticoagulation, higher levels of apolipoprotein A1 were independently associated with lower risk of ischemic cardiovascular outcomes, including stroke/systemic embolic event and mortality, and higher apolipoprotein B levels were associated with higher rates of myocardial infarction.

### What Are the Clinical Implications?

- These data provide a better understanding of the risks associated with dyslipidemia in patients with atrial fibrillation and suggest that investigating therapies targeting dyslipidemia may play a role in improving cardiovascular outcomes in atrial fibrillation.

cause mortality.<sup>5,6</sup> Other biomarkers, such as the marker for oxidative stress and inflammation, growth differentiation factor 15, have been reported to double the risk for major bleeding and death by approximately the same amount when elevated.<sup>7</sup> However, the predictive role of more-traditional biomarkers, such as those that are components of dyslipidemia, is less clear.

Dyslipidemia is known to promote atherosclerosis. It is a complex disease and is a major risk factor for adverse cardiovascular events.<sup>8–10</sup> High levels of low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL) are associated with myocardial infarction (MI) and stroke.<sup>11–13</sup> The relation between dyslipidemia and cardiovascular outcomes and its role as a risk factor in patients with AF treated with oral anticoagulation therapy have not been previously examined.

The aim of this substudy from the biomarker population of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial was therefore to assess the association between the concentration of apolipoprotein A1 (ApoA1), the main protein component of high-density lipoprotein (HDL), and apolipoprotein B (ApoB) the main protein component of LDL, at baseline and clinical outcomes after adjusting for cardiovascular risk factors as well as other relevant biomarkers that have shown prognostic value for adverse events in AF.<sup>5–7,14,15</sup>

## Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

## Population and Trial Design

The present study population consisted of participants from the ARISTOTLE trial; a multicenter, double-blind, double-dummy, randomized, clinical trial which enrolled 18 201 patients with AF and at least 1 additional risk factor for stroke or systemic embolism (systemic embolic event; SEE). The details and outcomes of the ARISTOTLE trial have been described and published previously.<sup>16,17</sup> All patients were randomized to receive either warfarin or apixaban for stroke prevention in a 1:1 fashion. The apolipoprotein biomarker substudy cohort comprised of the first included 14 884 patients, and the median length of follow-up was 1.9 years. Overall, the ARISTOTLE biomarker cohort was representative of the full study cohort and has been described in detail previously.<sup>18</sup> Approval by the appropriate ethics committees was obtained at all sites. All patients provided written informed consent.

## End Points

The primary outcome of this biomarker analysis was a composite of ischemic stroke, SEE, MI, and cardiovascular death. Other evaluated outcomes were the individual constituents of the composite ischemic outcome, all-cause mortality and major bleeding, according to the International Society on Thrombosis and Haemostasis criteria.<sup>16</sup> All outcomes were centrally adjudicated as previously described.<sup>16,17</sup>

## Biomarker Collection, Storage, and Laboratory Methods

Venous blood samples were obtained before study drug administration from enrolled patients in the biomarker study of the ARISTOTLE trial. Samples were stored in aliquots at  $-70^{\circ}\text{C}$  and subsequently transferred to the Clinical Chemistry Laboratory at Uppsala University Hospital (Uppsala, Sweden) for analysis. Apolipoproteins were analyzed using a particle-enhanced immunoturbidimetric assay (Abbott, Abbott Park, IL).

Analysis of high-sensitivity cardiac troponin T, N-terminal pro-B-type natriuretic peptide, growth-differentiation factor-15, cystatin C, interleukin 6 (IL-6), and C-reactive protein have been described in detail previously.<sup>5–7,14,15</sup>

## Statistical Analysis

In total, 14 884 patients in the ARISTOTLE study had apolipoproteins measured at baseline and were included in our analysis. Demographics and other baseline characteristics were summarized using frequencies for categorical variables

**Table 1.** Baseline Characteristics of Participants in Relation to ApoA1 Levels

	ApoA1 Level, g/L				P Value*
	≤0.94	>0.94 to 1.1	>1.1 to 1.3	>1.3	
n	3823	4521	3728	2812	
Age, y median (Q1, Q3)	70.0 (62.0, 76.0)	69.0 (62.0, 76.0)	70.0 (63.0, 76.0)	71.0 (64.0, 76.0)	<0.0001
Male	2823 (73.8%)	3085 (68.2%)	2329 (62.5%)	1347 (47.9%)	<0.0001
Weight, kg, median (Q1, Q3)	83.5 (70.4, 97.5)	84.0 (71.0, 98.0)	82.0 (70.0, 95.0)	78.5 (67.1, 90.0)	<0.0001
Permanent or persistent AF	3387 (88.6%)	3848 (85.2%)	3109 (83.4%)	2287 (81.3%)	<0.0001
Heart failure	1588 (41.5%)	1661 (36.7%)	1257 (33.7%)	833 (29.6%)	<0.0001
Hypertension	3327 (87.0%)	3957 (87.5%)	3277 (87.9%)	2467 (87.7%)	0.6897
Age ≥75 y	1142 (29.9%)	1329 (29.4%)	1169 (31.4%)	922 (32.8%)	<0.0001
Diabetes mellitus	1098 (28.7%)	1244 (27.5%)	806 (21.6%)	532 (18.9%)	<0.0001
Previous stroke or TIA	728 (19.0%)	860 (19.0%)	691 (18.5%)	514 (18.3%)	0.8122
MI	617 (16.1%)	575 (12.7%)	452 (12.1%)	269 (9.6%)	<0.0001
Previous PCI/CABG	594 (15.5%)	621 (13.7%)	490 (13.1%)	314 (11.2%)	<0.0001
Peripheral arterial disease	200 (5.2%)	227 (5.0%)	182 (4.9%)	115 (4.1%)	0.1714
Age 65 to 75 y	1467 (38.4%)	1767 (39.1%)	1448 (38.8%)	1153 (41.0%)	0.1606
CHA <sub>2</sub> DS <sub>2</sub> -VASc-score, median (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	0.0138
Aspirin	1289 (33.7%)	1441 (31.9%)	1087 (29.2%)	782 (27.8%)	<0.0001
ACEi or ARB	2766 (75.1%)	3224 (74.0%)	2636 (73.9%)	1941 (71.9%)	<0.0001
Beta-blocker	2558 (69.4%)	2935 (67.4%)	2384 (66.9%)	1678 (62.2%)	<0.0001
Calcium-channel blocker	1085 (29.4%)	1378 (31.6%)	1122 (31.5%)	962 (35.7%)	<0.0001
Digoxin	1374 (37.3%)	1494 (34.3%)	1105 (31.0%)	784 (29.1%)	<0.0001
Statin treatment	1644 (43.0%)	1941 (42.9%)	1633 (43.8%)	1246 (44.3%)	0.6069
Creatinine clearance (mL/min), median (Q1, Q3)	74.8 (57.2, 97.1)	75.3 (57.3, 98.8)	74.4 (57.3, 95.3)	71.1 (54.4, 89.4)	<0.0001
CRP (mg/L), median (Q1, Q3)	2.2 (1.0, 5.2)	2.4 (1.1, 5.2)	2.1 (1.0, 4.4)	2.1 (1.0, 4.3)	<0.0001
Cystatin C (mg/L), median (Q1, Q3)	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	<0.0001
GDF-15 (ng/L), median (Q1, Q3)	1477.0 (996.5, 2266.5)	1414.0 (985.5, 2155.5)	1310.0 (957.0, 1901.0)	1331.5 (978.0, 1875.2)	<0.0001
IL-6 (ng/L), median (Q1, Q3)	2.8 (1.8, 5.0)	2.4 (1.6, 4.1)	2.1 (1.4, 3.5)	2.0 (1.3, 3.1)	<0.0001
NT-proBNP (ng/L), median (Q1, Q3)	695.0 (361.0, 1258.5)	728.0 (367.0, 1293.0)	716.0 (364.0, 1237.2)	711.5 (356.0, 1204.2)	0.5783
cTnT-hs (ng/L), median (Q1, Q3)	11.5 (7.7, 17.9)	11.2 (7.6, 16.8)	10.7 (7.4, 16.1)	10.4 (7.4, 15.4)	<0.0001

ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ApoA1, apolipoprotein A1; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CHD, congestive heart disease; CrCL, creatinine clearance; CRP, C-reactive protein; cTnT-hs, high-sensitivity cardiac troponin T; GDF-15, growth differentiation factor 15; IL-6, interleukin 6; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; Q, quartile; TIA, transient ischemic attack.

\*Tests used: Pearson's  $\chi^2$  test for the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and for statin treatment, all other by the Kruskal–Wallis test.

and median and 25th and 75th percentiles for continuous variables. For tests of differences among groups, the  $\chi^2$  test was used for categorical variables and the Kruskal–Wallis test was used for continuous variables.

The association between baseline apolipoprotein levels and adverse outcomes was studied using multivariable Cox proportional-hazards models with apolipoprotein as continuous variables. Patients were followed until the respective event occurred or, if the event did not occur, were censored at

end of study or at death (for nonfatal outcomes). Results are presented showing hazard ratio per interquartile change, that is, identical to comparing the 75th with the 25th percentile, of the respective apolipoprotein sample distribution, or, in other words, a difference in apolipoprotein levels that contains the inner half of the sample values.<sup>19</sup> The first model (model 1) was adjusted for baseline characteristics and clinical risk factors; age, sex, body mass index, smoking status, systolic blood pressure, AF type, creatinine clearance, diabetes

**Table 2.** Baseline Characteristics of Participants in Relation to ApoB Levels

	ApoB Level, g/L				P Value*
	≤0.55	>0.55 to 0.7	>0.7 to 0.85	>0.85	
n	3747	3951	3504	3682	
Age, y, median (Q1, Q3)	72.0 (65.0, 78.0)	70.0 (64.0, 76.0)	69.0 (62.0, 75.0)	68.0 (60.0, 74.0)	<0.0001
Male	2511 (67.0%)	2583 (65.4%)	2195 (62.6%)	2294 (62.3%)	<0.0001
Weight, kg, median (Q1, Q3)	80.5 (68.0, 94.5)	82.0 (70.0, 95.3)	82.0 (70.0, 95.3)	83.5 (71.6, 97.0)	<0.0001
Permanent or persistent AF	3212 (85.7%)	3408 (86.3%)	2971 (84.8%)	3040 (82.6%)	<0.0001
Heart failure	1281 (34.2%)	1346 (34.1%)	1241 (35.4%)	1471 (40.0%)	<0.0001
Hypertension	3269 (87.2%)	3461 (87.6%)	3033 (86.6%)	3265 (88.7%)	0.0515
Age ≥75 y	1463 (39.0%)	1290 (32.6%)	977 (27.9%)	833 (22.6%)	<0.0001
Diabetes mellitus	1097 (29.3%)	1027 (26.0%)	823 (23.5%)	733 (19.9%)	<0.0001
Previous stroke or TIA	774 (20.7%)	775 (19.6%)	633 (18.1%)	613 (16.6%)	<0.0001
MI	647 (17.3%)	544 (13.8%)	354 (10.1%)	369 (10.0%)	<0.0001
Previous PCI/CABG	774 (20.7%)	636 (16.1%)	357 (10.2%)	252 (6.8%)	<0.0001
Peripheral arterial disease	211 (5.6%)	220 (5.6%)	140 (4.0%)	152 (4.1%)	0.0003
Age 65 to 75 y	1451 (38.7%)	1576 (39.9%)	1406 (40.1%)	1402 (38.1%)	<0.0001
CHA <sub>2</sub> DS <sub>2</sub> -VASc-score, median (Q1, Q3)	4.0 (3.0, 5.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	<0.0001
Aspirin	1657 (33.0%)	906 (30.7%)	1298 (29.9%)	733 (28.6%)	0.0003
ACEi or ARB	3577 (74.3%)	2060 (73.1%)	3087 (73.7%)	1831 (74.2%)	<0.0001
Beta-blocker	3105 (64.5%)	1866 (66.2%)	2851 (68.0%)	1721 (69.8%)	<0.0001
Calcium-channel blocker	1765 (36.7%)	896 (31.8%)	1242 (29.6%)	641 (26.0%)	<0.0001
Digoxin	1300 (27.0%)	909 (32.2%)	1503 (35.9%)	1043 (42.3%)	<0.0001
Statin treatment	2323 (62.0%)	1965 (49.7%)	1278 (36.5%)	898 (24.4%)	<0.0001
Creatinine clearance (mL/min), median (Q1, Q3)	70.0 (53.3, 90.0)	73.2 (56.3, 92.9)	75.4 (58.5, 96.7)	78.5 (60.1, 101.5)	<0.0001
CRP (mg/L), median (Q1, Q3)	1.6 (0.8, 3.8)	2.1 (1.0, 4.6)	2.4 (1.2, 5.2)	2.8 (1.4, 5.6)	<0.0001
Cystatin C (mg/L), median (Q1, Q3)	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)	<0.0001
GDF-15 (ng/L), median (Q1, Q3)	1520.0 (1050.0, 2319.0)	1457.0 (995.0, 2118.0)	1330.0 (966.8, 1965.0)	1256.0 (915.0, 1836.8)	<0.0001
IL-6 (ng/L), median (Q1, Q3)	2.5 (1.6, 4.1)	2.3 (1.5, 3.9)	2.3 (1.5, 3.8)	2.3 (1.5, 3.8)	<0.0001
NT-proBNP (ng/L), median (Q1, Q3)	740.0 (381.0, 1299.0)	739.0 (382.0, 1290.8)	701.0 (365.5, 1221.0)	672.5 (331.0, 1183.0)	<0.0001
cTnT-hs (ng/L), median (Q1, Q3)	11.6 (7.9, 17.7)	11.2 (7.6, 17.0)	10.6 (7.3, 15.9)	10.4 (7.3, 15.7)	<0.0001

ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ApoB, apolipoprotein B; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CHD, congestive heart disease; CrCL, creatinine clearance; CRP, C-reactive protein; cTnT-hs, high-sensitivity cardiac troponin T; GDF-15, growth differentiation factor 15; IL-6, interleukin 6; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; Q, quartile; TIA, transient ischemic attack.

\*Tests used: Pearson's  $\chi^2$  test for the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and for statin treatment, all other by the Kruskal–Wallis test.

mellitus, heart failure, previous stroke/systemic embolism (systemic embolic event; SEE)/transient ischemic attack, hypertension, use of warfarin within 7 days before randomization, randomized treatment (apixaban/warfarin), use of statin medication within 30 days before randomization, treatment at randomization with aspirin, treatment with angiotensin-converting enzyme inhibitors, or angiotensin II receptor blocker. The second Cox model (model 2) was

further adjusted for other prognostic biomarkers, all log-transformed: C-reactive protein, IL-6, high-sensitivity cardiac troponin T, cystatin C, and N-terminal pro-B-type natriuretic peptide. For the major bleeding outcome, additional adjustments were made for past bleeding and hemoglobin in model 2, and log-transformed growth differentiation factor 15 level in model 3. Kaplan–Meier estimates of the cumulative risk to the first occurrence of an event were plotted. All statistical

**Table 3.** Baseline Characteristics With the Strongest Association on ApoA1 Level

Variable	Comment	Ratio of Geometric Means (95% CI)	P Value
Age, y	10-y increase	1.039 (1.034, 1.045)	<0.0001
AF	Permanent vs persistent	0.962 (0.952, 0.973)	<0.0001
Creatinine clearance	100% increase	1.172 (1.158, 1.186)	<0.0001
Hemoglobin, g/dL	Per 1-g/dL increase	1.024 (1.022, 1.027)	<0.0001
IL-6	100% increase	0.954 (0.950, 0.958)	<0.0001
Sex	Male vs female	0.857 (0.850, 0.865)	<0.0001

The analysis is based on a model including all variables shown in Table 1. AF indicates atrial fibrillation; ApoA1, apolipoprotein A1; CI, confidence interval; IL-6, interleukin 6.

tests were 2-tailed and performed at the 0.05 significance level. Interaction between study treatment (apixaban or warfarin) and apolipoprotein level was analyzed using Cox proportional-hazards models including study treatment group, apolipoprotein, and treatment by apolipoprotein interaction as covariates. Given that statin therapy may affect ApoB levels substantially, sensitivity analyses were performed for the association of ApoB to outcomes in patients without any statin therapy at baseline (n=8420). Because all analyses were exploratory, there were no adjustments for multiple comparisons. The Biostatistics section at Uppsala Clinical Research Center conducted the statistical analyses.

## Results

Baseline demographics and clinical characteristics of the study population in relation to apolipoprotein levels are summarized in Tables 1 and 2. In summary, the median age

**Table 4.** Baseline Characteristics With the Strongest Association on ApoB Level

Variable	Comment	Ratio of Geometric Means (95% CI)	P Value
Creatinine clearance	100% increase	1.105 (1.088, 1.123)	<0.0001
GDF-15	100% increase	0.952 (0.945, 0.959)	<0.0001
Hemoglobin, g/dL	Per 1-g/dL increase	1.051 (1.048, 1.055)	<0.0001
IL-6	100% increase	0.959 (0.954, 0.964)	<0.0001
Sex	Male vs female	0.906 (0.896, 0.917)	<0.0001
Statin treatment	Yes vs no	0.856 (0.848, 0.865)	<0.0001

The analysis is based on a model including all variables shown in Table 1. ApoB indicates apolipoprotein B; CI, confidence interval; GDF-15, growth-differentiation factor-15; IL-6, interleukin 6.

was 70 years and ≈64% were male. The median (25th, 75th) ApoA1 concentration was 1.10 g/L (0.94, 1.30). For ApoB, the median (25th, 75th) was 0.70 g/L (0.55, 0.85). Most clinical characteristics, treatment, and risk factors for stroke were associated with both ApoA1 and ApoB. In multivariable models (Table 3), low levels of ApoA1 were most strongly associated with male sex, higher IL-6 levels, and permanent or persistent AF ( $P<0.0001$  for all). High levels of ApoA1 were most strongly associated with a better renal function, older age, and higher hemoglobin levels. For ApoB, low levels were more strongly associated with statin therapy, male sex, higher growth differentiation factor 15 levels, and higher IL-6 levels ( $P<0.0001$  for all; Table 4). High levels of ApoB were most strongly associated with a better renal function and higher hemoglobin levels ( $P<0.0001$  for both).

## Dyslipidemia in Relation to Composite Ischemic Outcome

There were a total of 883 events of the composite ischemic outcome consisting of ischemic stroke, SEE, MI, and cardiovascular death. Risk was substantially lower with higher baseline levels of ApoA1. In the fully adjusted analyses, ApoA1 was independently associated with a lower risk in the composite ischemic outcome with a hazard ratio (HR) of 0.81 (95% confidence interval [CI], 0.73–0.90;  $P<0.0001$ ) per interquartile change (Table 5).

ApoB was not statistically significantly associated with the risk of the composite ischemic outcome with an HR of 1.01 (95% CI, 0.92–1.12;  $P=0.8240$ ; Table 6).

Kaplan–Meier plots illustrating the associations between the apolipoproteins and the composite ischemic outcome are shown in Figures 1 and 2.

## Dyslipidemia and the Risk of Stroke or Systemic Embolism

In total, there were 397 occurrences of stroke or SEE during the trial follow-up. In the fully adjusted analyses, ApoA1 was independently associated with a lower risk of stroke or SEE with a HR of 0.84 (95% CI, 0.72–0.98;  $P=0.0248$ ) per interquartile change (Table 5). ApoB was not statistically significantly associated with stroke or SEE in any model (Table 6).

## Dyslipidemia and the Risk of MI

A total of 149 MI events were observed during follow-up. There was a lower risk of MI with higher baseline levels of ApoA1, however not statistically significant in any model (Table 5).

**Table 5.** Association of ApoA1 at Baseline With Outcomes According to Continuous Levels of ApoA1

	n	Events	Unadjusted		Adjusted Clinical Risk Factors		Adjusted Clinical+Biomarkers	
			HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Ischemic composite outcome	14 884	883 (3.13)	0.75 (0.69–0.82)	<0.0001	0.80 (0.72–0.87)	<0.0001	0.81 (0.73–0.90)	<0.0001
Stroke or systemic embolism	14 884	397 (1.41)	0.83 (0.73–0.95)	0.0080	0.83 (0.73–0.96)	0.0094	0.84 (0.72–0.98)	0.0248
MI	14 884	149 (0.52)	0.85 (0.68–1.06)	0.1522	0.89 (0.71–1.12)	0.3200	0.86 (0.67–1.10)	0.2356
Major bleeding	14 853	702 (2.74)	0.87 (0.78–0.96)	0.0065	0.91 (0.82–1.01)	0.0768	0.90 (0.80–1.01)	0.0724
Cardiovascular death	14 884	543 (1.88)	0.69 (0.61–0.77)	<0.0001	0.75 (0.66–0.84)	<0.0001	0.78 (0.68–0.89)	0.0002
Death	14 884	1068 (3.69)	0.69 (0.64–0.75)	<0.0001	0.73 (0.67–0.80)	<0.0001	0.77 (0.70–0.85)	<0.0001

Three different proportional hazards model have been used, 1 without any adjustment, 1 adjusted for randomized treatment, demographic, and clinical risk factors, and 1 adjusted for randomized treatment, demographic, and clinical risk factors plus biomarkers. The demographic and clinical risk factors used were: age, sex, body mass index, smoking status, systolic blood pressure, atrial fibrillation type, creatinine clearance, diabetes mellitus, heart failure, previous stroke/systemic embolic event/transient ischemic attack, hypertension, randomized treatment, use of warfarin within 7 days of randomization and use of statin medication within 30 days before randomization, treatment at randomization with aspirin, and treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker. The used biomarkers markers were high-sensitivity cardiac troponin T, N-terminal pro-B-type natriuretic peptide, cystatin C, C-reactive protein, and interleukin 6. For major bleeding, past bleeding and hemoglobin were added to model 1, and growth differentiation factor 15 to model 2. Cox models based on continuous biomarker levels showing hazard ratio per interquartile change (eg, Q3 vs Q1). ApoA1 indicates apolipoprotein A1; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

In the fully adjusted analyses, higher ApoB was independently associated with an increased risk of MI with an HR of 1.33 (95% CI, 1.06–1.68;  $P=0.0144$ ) per interquartile change.

### Dyslipidemia and the Risk of Mortality

During follow-up, a total of 1068 patients died from all causes, of which 543 died from cardiovascular causes. Higher levels of ApoA1 were statistically significantly associated with lower risk of all-cause and cardiovascular mortality, respectively. This association remained statistically significant in the model also adjusting for cardiovascular biomarkers with an HR of 0.77 (95% CI, 0.70–0.85;  $P<0.0001$ ) for all-cause mortality,

and an HR of 0.78 (95% CI, 0.68–0.89;  $P=0.0002$ ), for cardiovascular mortality, per interquartile change (Table 5).

In fully adjusted models, ApoB was associated with all-cause mortality with a higher risk in those with lower ApoB levels with an HR of 0.84 (95% CI, 0.76–0.92;  $P=0.0002$ ) hazard ratio per interquartile change. A similar association was observed for ApoB with cardiovascular death; however, this did not remain statistically significant in fully adjusted analyses (Table 6).

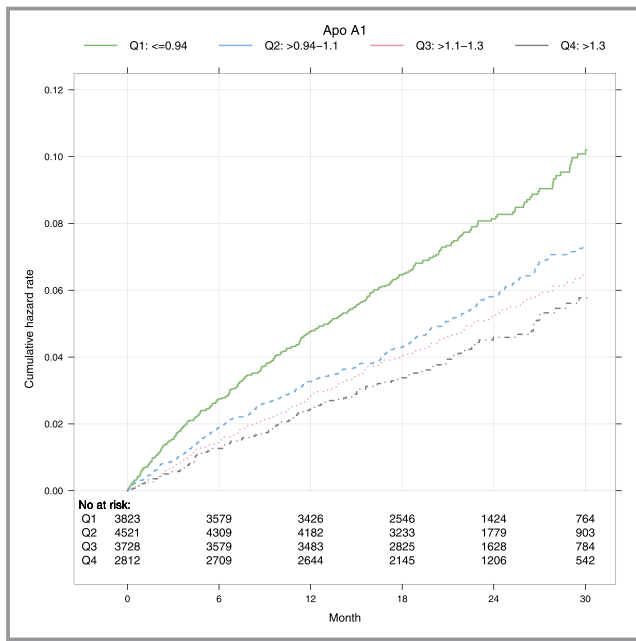
### Dyslipidemia and the Risk of Major Bleeding

A total of 702 major bleeding events were observed in this biomarker cohort. There was lower risk of major bleeding with

**Table 6.** Association of ApoB at Baseline With Outcomes According to Continuous Levels of ApoB

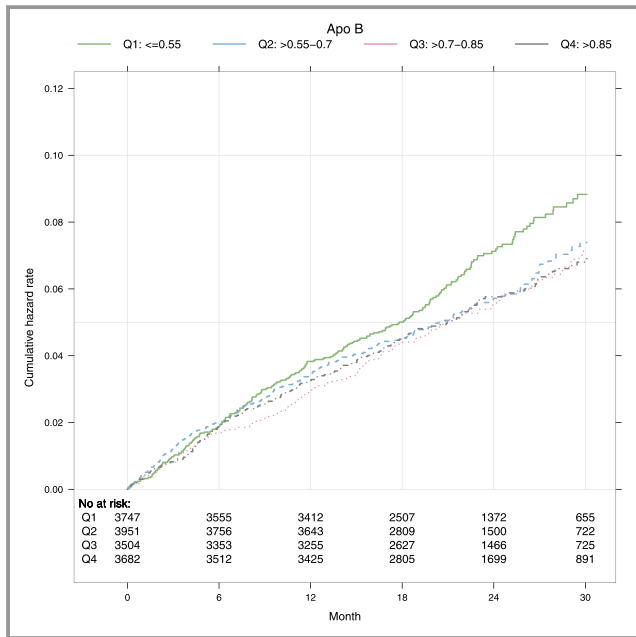
	n	Events	Unadjusted		Adjusted Clinical Risk Factors		Adjusted Clinical+Biomarkers	
			HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Ischemic composite outcome	14 884	883 (3.13)	0.94 (0.86–1.03)	0.1609	1.00 (0.91–1.10)	0.9841	1.01 (0.92–1.12)	0.8240
Stroke or systemic embolism	14 884	397 (1.41)	0.94 (0.83–1.07)	0.3722	1.02 (0.89–1.18)	0.7798	1.05 (0.90–1.21)	0.5564
MI	14 884	149 (0.52)	1.10 (0.89–1.35)	0.3685	1.37 (1.10–1.71)	0.0055	1.33 (1.06–1.68)	0.0144
Major bleeding	14 853	702 (2.74)	0.80 (0.72–0.88)	<0.0001	0.98 (0.87–1.10)	0.7562	0.98 (0.86–1.11)	0.7100
Cardiovascular death	14 884	543 (1.88)	0.87 (0.78–0.98)	0.0170	0.88 (0.78–0.99)	0.0357	0.89 (0.79–1.02)	0.0839
Death	14 884	1068 (3.69)	0.81 (0.74–0.88)	<0.0001	0.84 (0.77–0.92)	0.0002	0.84 (0.76–0.92)	0.0002

Three different proportional hazards model have been used, 1 without any adjustment, 1 adjusted for randomized treatment, demographic, and clinical risk factors, and 1 adjusted for randomized treatment, demographic, and clinical risk factors plus biomarkers. The demographic and clinical risk factors used were: age, sex, body mass index, smoking status, systolic blood pressure, atrial fibrillation type, creatinine clearance, diabetes mellitus, heart failure, previous stroke/systemic embolic event/transient ischemic attack, hypertension, randomized treatment, use of warfarin within 7 days of randomization and use of statin medication within 30 days before randomization, treatment at randomization with aspirin, and treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker. The used biomarkers markers were high-sensitivity cardiac troponin T, N-terminal pro-B-type natriuretic peptide, cystatin C, C-reactive protein, and interleukin 6. For major bleeding, past bleeding and hemoglobin were added to model 1 and growth differentiation factor 15 to model 2. Cox models based on continuous biomarker levels showing hazard ratio per interquartile change (eg, Q3 vs Q1). ApoB indicates apolipoprotein B; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.



**Figure 1.** Cumulative hazard rates for the composite ischemic outcome by quartiles of ApoA1. ApoA1 indicates apolipoprotein A1; Q, quartile.

higher ApoA1 levels. However, none of the apolipoproteins remained significantly associated with major bleeding in fully adjusted models (Tables 5 and 6).



**Figure 2.** Cumulative hazard rates for the composite ischemic outcome by quartiles of ApoB. ApoB indicates apolipoprotein B; Q, quartile.

## Sensitivity Analysis

Sensitivity analyses for the association of ApoB with cardiovascular outcomes in patients without statin therapy ( $n=8420$ ) overall showed similar results (Table 7). Additional sensitivity analyses for ApoB showed that the association with all-cause mortality was primarily driven by noncardiovascular death (Table 8), of which malignancy and infection were the most common causes of death.

## Outcomes According to Dyslipidemia and Randomized Treatment

The study treatment (apixaban or warfarin) interaction by apolipoprotein levels for the composite ischemic outcome was not statistically significant. For major bleeding, apixaban showed a greater relative risk reduction in those with high ApoB levels ( $P=0.0234$ ), with a similar result for ApoA1 ( $P=0.0584$ ; Figures 3 and 4).

## Discussion

In patients with AF on oral anticoagulation, higher levels of ApoA1 were associated with lower risk of composite ischemic outcomes, stroke, and death even after adjustment for baseline characteristics, comorbidities, other biomarkers, and medications. Higher levels of ApoB were associated with higher rates of MI only, but not with the other cardiovascular outcomes. In contrast, lower levels of ApoB were associated with an increased risk of all-cause death. Importantly, both apolipoproteins remained statistically significantly associated with these outcomes even after adjustment for other prognostic biomarkers (high-sensitivity cardiac troponin T, N-terminal pro-B-type natriuretic peptide, cystatin C, C-reactive protein, and IL-6). Furthermore, among those with higher apolipoprotein levels, apixaban showed an even greater relative risk reduction of major bleeding than in patients with lower levels of these apolipoproteins.

Dyslipidemia is a complex disease and a traditional risk factor for adverse cardiovascular events. Other than a possible association between dyslipidemia and incidence of AF, its relationship with AF has not been well described before.<sup>20–26</sup> To our knowledge, this is the first study showing that plasma levels of apolipoproteins were independently associated with major cardiovascular events in anticoagulated patients with AF. In this study, high baseline ApoA1 levels were associated with  $\approx 15\%$  lower risk of stroke or SEE, 20% reduced risk for cardiac and all-cause mortality, and similar association to composite ischemic outcomes. High levels of ApoB, on the other hand, were associated with 30% increased the risk of MI. These associations, similar to that of dyslipidemia in coronary artery disease, might be explained by the atherogenic properties of dyslipidemia.<sup>27–30</sup>

**Table 7.** Association of ApoB at Baseline With Outcomes According to Continuous Levels of ApoB Showing the Hazard Ratio Per Interquartile Change in Patients Without Statin Treatment

	n	Events	Unadjusted		Adjusted Clinical Risk Factors		Adjusted Clinical+Biomarkers	
			HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Ischemic composite outcome	8420	515 (3.22)	0.88 (0.78–0.99)	0.0327	0.95 (0.85–1.09)	0.4161	0.96 (0.85–1.09)	0.5601
Stroke or systemic embolism	8420	220 (1.37)	0.87 (0.73–1.04)	0.1178	0.95 (0.79–1.14)	0.5757	0.98 (0.81–1.19)	0.8310
MI	8420	70 (0.43)	1.29 (0.96–1.73)	0.0908	1.36 (1.01–1.84)	0.0447	1.29 (0.94–1.78)	0.1161
Major bleeding	8409	365 (2.52)	0.82 (0.71–0.94)	0.0051	0.99 (0.86–1.15)	0.9290	0.98 (0.84–1.16)	0.8403
Cardiovascular death	8420	343 (2.09)	0.79 (0.68–0.91)	0.0015	0.86 (0.74–0.99)	0.0372	0.87 (0.74–1.02)	0.0783
Death	8420	655 (3.99)	0.74 (0.67–0.82)	<0.0001	0.81 (0.73–0.91)	0.0002	0.81 (0.72–0.90)	0.0002

Three different proportional hazards model have been used, 1 without any adjustment, 1 adjusted for randomized treatment, demographic, and clinical risk factors, and 1 adjusted for randomized treatment, demographic, and clinical risk factors plus biomarkers. The demographic and clinical risk factors used were: age, sex, body mass index, smoking status, systolic blood pressure, atrial fibrillation type, creatinine clearance, diabetes mellitus, heart failure, previous stroke/systemic embolic event/transient ischemic attack, hypertension, randomized treatment, use of warfarin within 7 days of randomization and use of statin medication within 30 days before randomization, treatment at randomization with aspirin, and treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker. The used biomarkers markers were high-sensitivity cardiac troponin T, N-terminal pro-B-type natriuretic peptide, cystatin C, C-reactive protein, and interleukin 6. For major bleeding, past bleeding and hemoglobin were added to model 1 and growth differentiation factor 15 to model 2. Cox models based on continuous biomarker levels showing hazard ratio per interquartile change (eg, Q3 vs Q1). ApoB indicates apolipoprotein B; CI, confidence interval; HR, hazard ratio.

An important finding in this study is the association between dyslipidemia and mortality for both ApoA1 and ApoB. Similar to low HDL levels, low ApoA1 conferred higher risk of death. However, for ApoB, the all-cause mortality rate was paradoxically higher in patients with lower ApoB concentrations. Similar findings have been presented in other cohorts as well.<sup>31,32</sup> In a large, prospective, observational study of patients following an acute MI, an increased risk of all-cause mortality was shown in the group with the lowest levels of LDL cholesterol.<sup>31</sup> Increased rate of all-cause mortality has also been associated with low levels of LDL cholesterol in the elderly.<sup>32</sup> Plasma cholesterol levels decline with age, malnutrition, chronic disease, and even with inflammation.<sup>32–35</sup> This “lipid paradox” in which patients with the lowest levels of LDL cholesterol, or in this case ApoB, are at an increased risk for all-cause mortality could thus possibly be explained, at least in part, by a higher disease burden and frailty. Patients in this study in the lowest ApoB quartile were, in fact, more comorbid, perhaps best illustrated by higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, and were therefore likely at an increased risk for death. Similar patterns were also observed in the multivariable models and in sensitivity analyses in patients not on statin therapy.

Women in this study had higher levels of ApoA1 and lower levels of ApoB (Tables 1 and 2). These findings are consistent

with previous studies.<sup>36</sup> However, in the adjusted Cox analyses, the associations between the studied apolipoproteins with outcomes are adjusted for sex apolipoprotein differences. Thus, sex should not influence the apolipoprotein association with outcomes.

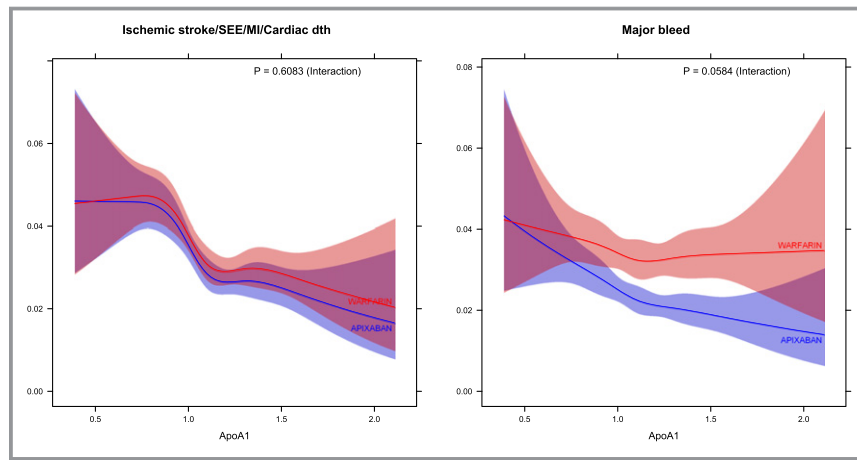
The relationship between dyslipidemia and stroke is complex because the association seems to vary dependent on stroke subtype as well as lipid parameter studied.<sup>13,37</sup> Most observational studies have shown an association between higher levels of LDL cholesterol and lower levels of HDL cholesterol with increased ischemic stroke risk.<sup>13</sup> Few studies have, however, evaluated dyslipidemia in relation to stroke risk in an AF population on oral anticoagulation. Recently, in a small cohort of AF patients without anticoagulant therapy, high LDL cholesterol was found to be an independent predictor of ischemic stroke.<sup>38</sup> In the present study, no such findings were observed, which may be attributable to a relatively lower event rate which in turn is attributed to the fact that all patients received oral anticoagulants. Low ApoA1 levels were, on the other hand, associated with higher stroke/SEE rates and even more so to the composite ischemic outcome. This could indicate that ApoA1 indeed may play a role in the pathophysiology of ischemic outcomes in AF. Furthermore, a greater relative risk reduction of major bleedings was observed with

**Table 8.** Association of ApoB at Baseline With Noncardiovascular Death According to Continuous Levels of ApoB Showing the Hazard Ratio Per Interquartile Change in All Patients and in Patients Without Statin Treatment

	n	Events	Unadjusted		Adjusted Clinical Risk Factors		Adjusted Clinical+Biomarkers	
			HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
All	14 884	525 (1.82)	0.74 (0.66–0.84)	<0.0001	0.81 (0.71–0.92)	0.0015	0.79 (0.69–0.90)	0.0005
Without statin medication	8420	312 (1.90)	0.69 (0.59–0.80)	<0.0001	0.77 (0.66–0.91)	0.0015	0.75 (0.63–0.88)	0.0006

ApoB indicates apolipoprotein B; CI, confidence interval; HR, hazard ratio.





**Figure 3.** One-year event rates for continuous level of ApoA1 according to randomized treatment. ApoA1 indicates apolipoprotein A1; Cardiac dth, cardiac death; MI, myocardial infarction; SEE, systemic embolic event.

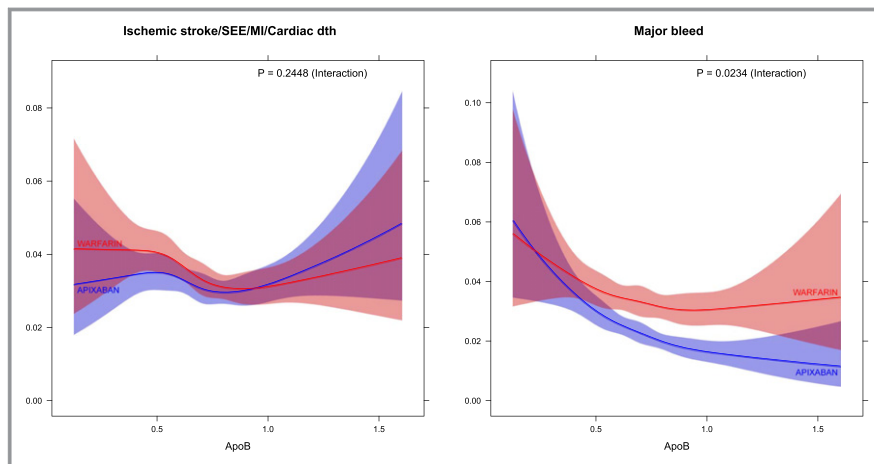
apixaban compared with warfarin in patients with higher levels of apolipoprotein. In these individuals, apixaban may be an even more-attractive choice than warfarin. The underlying mechanism for the treatment interaction is, however, unclear and warrants further investigation.

Several biomarkers have, in recent studies, shown to significantly improve the prognostication for stroke in AF.<sup>39–41</sup> They could therefore lead to a better understanding of AF and its associated adverse outcomes, improve risk stratification, and, potentially, create new therapeutic approaches to reduce morbidity and mortality.

The findings from the present study indicate that dyslipidemia, a traditional cardiovascular risk factor, may play a role in AF-related adverse outcomes. Therapeutic interventions for dyslipidemia could therefore prove beneficial effects in reducing the risk of these complications. In clinical practice, however, most drugs that increase ApoA1/HDL cholesterol

(such as niacin and fibrates) have so far not been able to show further reduction in cardiovascular events.<sup>42,43</sup> It is possible that newer agents, such as cholesteryl ester transfer protein inhibitors, may be more favorable.<sup>44</sup> The medications, however, have not been studied specifically in patients with AF, and any potential beneficial effect of these agents on AF burden and associated outcomes need to be tested in future prospective trials and may possibly also need stratification according to genetic variances.<sup>45</sup> Another issue that warrants mentioning is that only half (51.6%) of the patients with AF and a traditional indication for statin therapy (eg, established vascular disease or diabetes mellitus) was on statin treatment in the study cohort. Better adherence to existing guidelines for management of dyslipidemia may thus also be an important factor in the efforts to improve outcomes in AF.

Even though the statistical analyses were adjusted for a variety of cardiovascular risk factors, patient background



**Figure 4.** One-year event rates for continuous level of ApoB according to randomized treatment. ApoB indicates apolipoprotein B; Cardiac dth, cardiac death; MI, myocardial infarction; SEE, systemic embolic event.

characteristics, and cardiovascular biomarkers, residual confounding cannot be excluded. Information of pre-existing hyperlipidemia per se was not collected within the ARISTOTLE trial, neither were traditional markers of hyperlipidemia (cholesterol or triglyceride levels). Furthermore, the observational nature of this study shows associations and does not permit any deductions concerning causal relationships between dyslipidemia and AF.

## Conclusions

In patients with AF treated with oral anticoagulation, higher levels of ApoA1 were independently associated with lower risk of ischemic cardiovascular outcomes, including stroke/SEE and mortality. Higher ApoB levels were associated with higher rates of MI, but, paradoxically, lower risk of all-cause mortality. The benefits of apixaban over warfarin were consistent, regardless of the levels of ApoA1 and ApoB. Our findings provide unique insights to the interaction between AF and lipoproteins, and suggest that investigating therapies targeting dyslipidemia may play a role in improving cardiovascular outcomes in patients with AF.

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## Disclosures

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