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N-Terminal Pro–B-Type Natriuretic Peptide for Risk Assessment in Patients With Atrial Fibrillation

Insights From the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation)

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Objectives This study sought to assess the prognostic value of N-terminal pro–B-type natriuretic peptide (NT-proBNP) in patients with atrial fibrillation (AF) enrolled in the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial, and the treatment effect of apixaban according to NT-proBNP levels.

Background Natriuretic peptides are associated with mortality and cardiovascular events in several cardiac diseases.

Methods In the ARISTOTLE trial, 18,201 patients with AF were randomized to apixaban or warfarin. Plasma samples at randomization were available from 14,892 patients. The association between NT-proBNP concentrations and clinical outcomes was evaluated using Cox proportional hazard models, after adjusting for established cardiovascular risk factors.

Results Quartiles of NT-proBNP were: Q1, ≤363 ng/l; Q2, 364 to 713 ng/l; Q3, 714 to 1,250 ng/l; and Q4, >1,250 ng/l. During 1.9 years, the annual rates of stroke or systemic embolism ranged from 0.74% in the bottom NT-proBNP quartile to 2.21% in the top quartile, an adjusted hazard ratio of 2.35 (95% confidence interval [CI]: 1.62 to 3.40; $p < 0.0001$). Annual rates of cardiac death ranged from 0.86% in Q1 to 4.14% in Q4, with an adjusted hazard ratio of 2.50 (95% CI: 1.81 to 3.45; $p < 0.0001$). Adding NT-proBNP levels to the CHA_2DS_2VASc score improved C-statistics from 0.62 to 0.65 ($p = 0.0009$) for stroke or systemic embolism and from 0.59 to 0.69 for cardiac death ($p < 0.0001$). Apixaban reduced stroke, mortality, and bleeding regardless of the NT-proBNP level.

Conclusions NT-proBNP levels are often elevated in AF and independently associated with an increased risk of stroke and mortality. NT-proBNP improves risk stratification beyond the CHA_2DS_2VASc score and might be a novel tool for improved stroke prediction in AF. The efficacy of apixaban compared with warfarin is independent of the NT-proBNP level. (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation [ARISTOTLE]; NCT00412984)
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Atrial fibrillation (AF) increases the risk of stroke and death and consequently constitutes a significant societal health and economic problem (1,2). Prediction of a patient's risk of stroke is most commonly made using a clinical score such as the $CHADS_2$ or CHA_2DS_2VASc (heart failure, hypertension, age 75 years and older, diabetes, and previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category [female sex], respectively) (3,4). B-type natriuretic peptides are secreted by myocytes in response to a number of stimuli including an increase in wall stress (5). Their secretion increases with aging and with left ventricular hypertrophy and in acute coronary syndromes, heart failure, chronic kidney disease, and AF (6,7). In these conditions, N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a powerful predictor of prognosis (8–15). However, little is known about the predictive value of NT-proBNP in patients with AF in whom, at present, risk stratification based on clinical scores only offers a modest discriminating ability for the individual patients (4).

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In the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial (16), we obtained plasma samples for central biomarker analyses from 14,892 of 18,201 patients. In this pre-specified substudy, we examined whether NT-proBNP might predict the occurrence of stroke and other nonfatal and fatal cardiovascular events in anticoagulated patients with AF and an increased risk of stroke. We further tested the incremental value of measuring NT-proBNP levels in addition to established risk factors (including the CHA_2DS_2VASc score) to predict cardiovascular and bleeding events.

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
HR = hazard ratio
IDI = integrated discrimination improvement
ISTH = International Society on Thrombosis and Haemostasis
NRI = net reclassification improvement
NT-proBNP = N-terminal pro-B-type natriuretic peptide

Methods

The ARISTOTLE trial. The details of the ARISTOTLE trial were published previously (16). Briefly, the ARISTOTLE trial was a double-blind, double-dummy, randomized clinical trial that enrolled 18,201 patients with AF and at least 1 $CHADS_2$ risk factor for stroke or systemic embolism. Patients were randomized to warfarin (n = 9,081) or apixaban (n = 9,120). The primary endpoint was stroke or systemic embolism. Bleeding was classified according to the International Society on Thrombosis and Haemostasis (ISTH) criteria. The median length of follow-up was 1.9 years in the biomarker study.

Endpoints and clinical risk classification. The endpoints in the ARISTOTLE trial included stroke or systemic embolism; ischemic stroke and systemic embolism, hemorrhagic stroke, myocardial infarction; all-cause mortality; cardiac death (excluding bleeding and other noncardiac causes); ISTH major bleeding; and composites including stroke or systemic embolism, total death or cardiac death, and myocardial infarction. All endpoints were adjudicated by a blinded clinical events committee using pre-specified criteria (16). $CHADS_2$ and CHA_2DS_2VASc scores were calculated for each patient based on the sum of the corresponding risk factors present at randomization. Patients were categorized by $CHADS_2$ according to score (0 to 1, 2, or $\geq$3) and by CHA_2DS_2VASc scores (0 to 1, 2, 3, 4, and $\geq$5).

Biochemical methods. For the ARISTOTLE biomarker substudy, baseline blood samples were obtained from 14,892 patients. Plasma was frozen in aliquots and stored at −70°C until analyzed centrally. The NT-proBNP levels were determined with sandwich immunoassays on the Cobas Analytics e601 Immunoanalyzers (Roche Diagnostics, Mannheim, Germany) according to manufacturer instructions. The lower limit of detection for NT-proBNP with this assay is 5 ng/l. The analytical range extends from 20 to 35,000 ng/l according to the manufacturer. The upper reference level (97.5th percentile) in men and women 40 to 65 years of age is 184 and 268 ng/l, respectively, and 66 to 76 years of age, 269 and 391 ng/l, respectively (17). The lowest concentration with a coefficient of variation <10% is 30 ng/l (18).

Statistical analyses. These analyses included the 14,892 patients who provided blood samples for the biomarker study at randomization and also had available results of the evaluated biomarkers. Demographics and other baseline characteristics were summarized using frequencies for categorical variables and median and 25th and 75th percentiles for continuous variables. For tests of differences among

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groups, the chi-square test was used for categorical variables and the Kruskal-Wallis test was used for continuous variables.

Multivariable analysis of variance with natural logarithms of NT-proBNP as response variables and categorized baseline characteristics as explanatory variables was used to investigate the independent effect of each variable. Geometric means, calculated by antilogs of the model-adjusted means, were compared.

Efficacy analyses included all randomized patients and included all events from randomization until the efficacy cut-off date (pre-defined as January 30, 2011). Bleeding analyses were 'on treatment' including all randomized patients who received at least 1 dose of study drug and included all events from receipt of the study drug until 2 days after the last dose of the study drug.

The relationship between NT-proBNP and outcomes was evaluated both in a simple and multivariable Cox regression analysis. The multivariable analyses included established risk factors (age, sex, body mass index, smoking status, systolic blood pressure, heart rate, AF type, diabetes, heart failure, previous stroke/systemic embolism/transient ischemic attack, hypertension, previous myocardial infarction, previous peripheral arterial disease, coronary artery bypass grafting/percutaneous coronary intervention, treatment at randomization with aspirin, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, and amiodarone), randomized treatment, region, use of warfarin within 7 days before randomization, use of statin medication within 30 days before randomization score, and biomarkers (cystatin C and high-sensitivity troponin T). For the major bleeding endpoint, a history of anemia and of spontaneous or clinical relevant bleeding was also included in the established risk factors and the multivariable analysis. The hazard ratios (HRs) and 95% confidence intervals (CIs), using the group with the lowest biomarker levels as reference, were reported. The assumption of proportional hazards for the factors included in the Cox regression analyses was assessed visually using log-cumulative hazard plots (not shown).

Treatment effects were compared according to the NT-proBNP group using a Cox proportional hazards model including treatment group, NT-proBNP quartile group, and treatment by NT-proBNP interaction as covariates. The treatment HRs are reported at each level of NT-proBNP, regardless of the significance of interaction.

The incidences of the different endpoints were summarized in relation to randomized treatment, quartiles of the NT-proBNP level, and CHA_2DS_2VASc scores.

The increased discriminative values of adding NT-proBNP level to models with only a CHA_2DS_2VASc score and study treatment were investigated by estimating the difference in C-statistics between models with and without NT-proBNP levels and also the integrated discrimination improvement measure (IDI), as described by Pencina et al. (19,20). In these analyses, the occurrence/nonoccurrence of an event during the follow-up period was used as a binary response, and the C value will be the same as the area under the receiver-operating characteristic curve. The relative IDI was calculated to facilitate interpretation of the IDI (21). In addition, continuous (category-free) net reclassification improvement (NRI) was analyzed as a measure of probability of better reclassification minus the probability of worse reclassification with the new model. The NRI among events and nonevents as well as the total NRI were analyzed.

Kaplan-Meier estimates of the cumulative risk to the first occurrence of an event were calculated and plotted. Event rates per 100 patient-years of follow-up were reported. All statistical tests were 2 tailed and performed at the 0.05 significance level. There were no adjustments for multiple comparisons. The Clinical Trials section at Uppsala Clinical Research Center conducted the statistical analyses, using the statistical software package SAS, version 9.3 for Windows (SAS Institute, Cary, North Carolina) for all analyses.

Results

Baseline characteristics and distribution levels of NT-proBNP. The median NT-proBNP concentration was 714 ng/l (25th and 75th percentiles = 363 and 1,250 ng/l), and there was no difference between the warfarin and apixaban groups. The 25th percentile value was close to the upper reference level of NT-proBNP in healthy subjects (i.e., 75% of patients had an elevated level) (17).

Baseline characteristics according to NT-proBNP quartiles are shown in Table 1. Many characteristics were associated with NT-proBNP in univariate analysis, with higher levels in older subjects and women and in patients with other cardiovascular disease, diabetes, and renal dysfunction. NT-proBNP was also related to AF type. These baseline characteristics remained associated with the NT-proBNP level in a multivariable analysis ($p < 0.05$ for all). The strongest relationship was with AF type, with a more than 3-fold higher geometric mean NT-proBNP in patients with persistent/permanent AF compared with paroxysmal AF (ratio of geometric means: 3.35; 95% CI: 3.22 to 3.50; $p < 0.0001$), followed by reduced creatinine clearance (Cockcroft-Gault), heart failure, and age as independent predictors of NT-proBNP levels ($p < 0.0001$ for all). Patients with higher $CHADS_2$ and CHA_2DS_2VASc scores had higher NT-proBNP levels. Among patients in the highest quartile of NT-proBNP level >1,250 ng/l, 81.5% had a CHA_2DS_2VASc score >2 in contrast to only 59% in the lowest quartile of patients with NT-proBNP level ≤363 ng/l.

NT-proBNP in relation to outcomes and study treatment. In this substudy cohort, a total of 397 patients (1.40%/year) experienced stroke or systemic embolism, and 1,075 (3.69%/year) died; 547 (1.88%/year) died of a cardiac cause and 674 (2.61%/year) experienced a major bleeding episode during a median follow-up of 1.9 years. Higher baseline NT-proBNP concentration was strongly associated

Table 1 Demographics and Baseline Characteristics by Quartiles of NT-proBNP Level at Baseline

	NT-proBNP Level				
	≤363 ng/l	364-713 ng/l	714-1,250 ng/l	>1,250 ng/l	p Value
n	3,725	3,721	3,724	3,722	
Age, yrs	66.0 (59.0, 73.0)	69.0 (62.0, 75.0)	71.0 (65.0, 77.0)	73.0 (66.0, 79.0)	<0.0001
Male	2,522 (67.7)	2,519 (67.7)	2,339 (62.8)	2,210 (59.4)	<0.0001
Weight, kg	85.0 (73.4, 99.0)	85.0 (72.0, 99.0)	82.0 (70.0, 95.0)	76.4 (65.0, 89.1)	<0.0001
Permanent or persistent atrial fibrillation	2,215 (59.5)	3,384 (91.0)	3,516 (94.4)	3,522 (94.7)	<0.0001
Calculated CrCl, ml/min	85.0 (66.9, 109.7)	79.3 (62.0, 101.0)	72.3 (56.8, 90.5)	60.2 (45.6, 78.0)	<0.0001
$CHADS_2$ risk factors					
CHF or LVEF ≤40%	964 (25.9)	1,158 (31.1)	1,370 (36.8)	1,848 (49.7)	<0.0001
Hypertension	3,320 (89.1)	3,273 (88.0)	3,277 (88.0)	3,165 (85.0)	<0.0001
Age ≥75 yrs	718 (19.3)	1,006 (27.0)	1,293 (34.7)	1,549 (41.6)	<0.0001
Diabetes mellitus	829 (22.3)	986 (26.5)	1,173 (31.5)	1,620 (43.5)	<0.0001
Previous stroke or TIA	641 (17.2)	692 (18.6)	687 (18.4)	775 (20.8)	0.0009
CHA_2DS_2VASc risk factors					
MI	368 (9.9)	396 (10.6)	497 (13.3)	652 (17.5)	<0.0001
Previous PCI/CABG	394 (10.6)	478 (12.8)	549 (14.7)	599 (16.1)	<0.0001
PAD	128 (3.4)	159 (4.3)	204 (5.5)	234 (6.3)	<0.0001
Age 65–74 yrs	1,402 (37.6)	1,509 (40.6)	1,549 (41.6)	1,378 (37.0)	<0.0001
Female	1,203 (32.3)	1,202 (32.3)	1,385 (37.2)	1,512 (40.6)	<0.0001
$CHADS_2$ score					
≤1	1,600 (43.0)	1,348 (36.2)	1,174 (31.5)	935 (25.1)	<0.0001
2	1,257 (33.7)	1,321 (35.5)	1,386 (37.2)	1,403 (37.7)	
≥3	868 (23.3)	1,052 (28.3)	1,164 (31.3)	1,384 (37.2)	
CHA_2DS_2VASc–score					
≤1	524 (14.1)	370 (9.9)	227 (6.1)	178 (4.8)	<0.0001
2	1,002 (26.9)	895 (24.1)	689 (18.5)	513 (13.8)	
3	973 (26.1)	944 (25.4)	1,022 (27.4)	929 (25.0)	
4	685 (18.4)	765 (20.6)	889 (23.9)	961 (25.8)	
5	541 (14.5)	747 (20.1)	897 (24.1)	1,141 (30.7)	
Medications					
Aspirin	1,179 (31.7)	1,108 (29.8)	1,112 (29.9)	1,205 (32.4)	0.0313
Warfarin	1,851 (49.8)	2,102 (56.6)	2,146 (57.8)	1,901 (51.2)	<0.0001
ACE inhibitor or ARB	2,575 (69.1)	2,600 (69.9)	2,650 (71.2)	2,710 (72.8)	0.0028
Calcium-channel blocker	1,242 (33.3)	1,269 (34.1)	1,139 (30.6)	902 (24.2)	<0.0001
Beta-blocker	1,962 (52.7)	2,253 (60.5)	2,517 (67.6)	2,684 (72.1)	<0.0001
Digoxin	795 (21.3)	1,191 (32.0)	1,317 (35.4)	1,523 (40.9)	<0.0001

Values are n, median (Q1, Q3), or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; CHF = congestive heart failure; CrCl = creatinine clearance; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP =N-terminal pro–B-type natriuretic peptide PAD = peripheral artery disease; PCI = percutaneous coronary intervention; Q = quartile; TIA = transient ischemic attack.

with each of the major clinical outcomes examined except major bleeding, even after adjustment for the multivariable model (Fig. 1). For example, the annualized rate of stroke or systemic embolism ranged from 0.74% in the bottom NT-proBNP quartile (Q1: ≤363 ng/l) to 2.21% in the top quartile (Q4: >1,250 ng/l); adjusted HR (Q4 vs. Q1): 2.35; 95% CI: 1.62 to 3.40; $p < 0.0001$) (Fig. 1). The adjusted HR (Q4 vs. Q1) for all-cause mortality was 2.25 (95% CI: 1.80 to 2.81, $p < 0.0001$), and for cardiac mortality, it was 2.50 (95% CI: 1.81 to 3.45, $p < 0.0001$). Higher NT-proBNP was not associated with an increased risk of major bleeding (adjusted HR [Q4 vs. Q1]: 1.07; 95% CI: 0.82 to 1.40; $p = 0.0667$).

There was no significant interaction between baseline NT-proBNP levels and the effect of randomized treatment in relation to any of these or the other study outcomes (Fig. 2). Kaplan-Meier plots illustrating the associations between NT-proBNP (by quartile) and these outcomes are shown in Figure 3.

NT-proBNP levels in relation to CHA_2DS_2VASc score for risk assessment and prognostic discrimination. Annual rates of stroke or systemic embolism according to NT-proBNP levels and CHA_2DS_2VASc score are illustrated in Figure 4A. The rate increased with both increasing CHA_2DS_2VASc score and higher NT-proBNP level. The highest annual rate of stroke and systemic embolism (2.45%) was found in the group with a CHA_2DS_2VASc score ≥3 and an NT-proBNP concentration >1,250 ng/l, compared with an average annual rate of 0.56% in patients with a CHA_2DS_2-VASc score ≤2 and NT-proBNP levels ≤363 ng/l. Adding

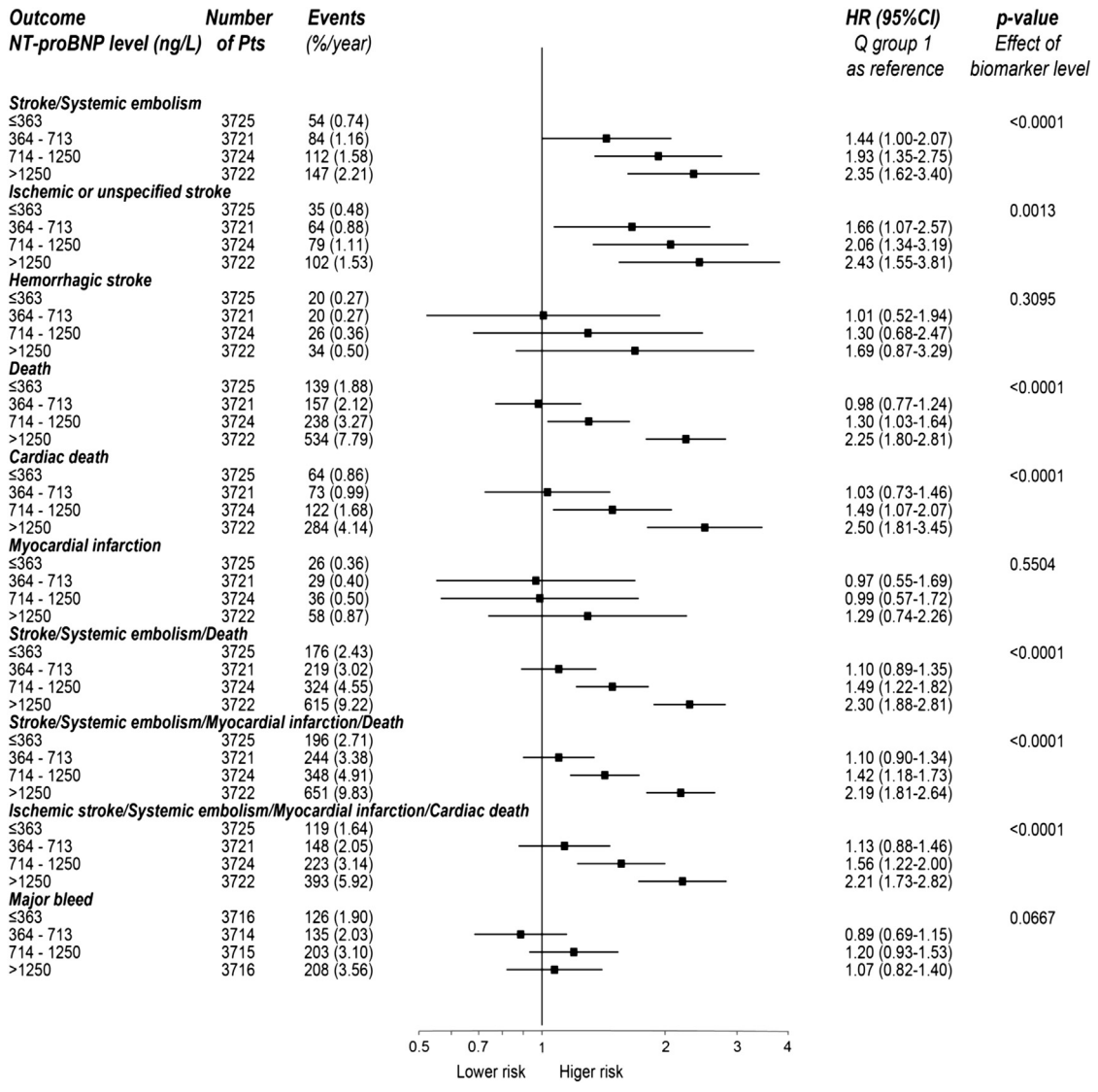

Figure 1 **Impact of Quartiles of NT-proBNP at Baseline on Outcomes**

Cox proportional hazards model adjusted for established risk factors (age, sex, body mass index, smoking status, systolic blood pressure, heart rate, atrial fibrillation type, diabetes, heart failure, previous stroke/composite of stroke and systemic embolism/transient ischemic attack, hypertension, previous myocardial infarction, previous peripheral artery disease/coronary artery bypass graft/percutaneous coronary intervention, treatment at randomization with aspirin, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and amiodarone for the major bleeding endpoint; history of anemia and of spontaneous or clinical relevant bleeding were also included), randomized treatment, region, use of warfarin within 7 days before randomization, use of statin medication within 30 days before randomization score and biomarkers (cystatin C and high-sensitivity troponin T). CI = confidence interval; HR = hazard ratio; NT-proBNP = N-terminal pro–B-type natriuretic peptide; Pts = patients; Q = quartile.

NT-proBNP to the CHA_2DS_2VASc score improved the predictive model, with an increase in the C-statistic from 0.620 (95% CI: 0.592 to 0.647) to 0.646 (95% CI: 0.619 to 0.673) ($p = 0.0009$) and a relative IDI improvement of 47% (IDI: 0.0023; 95% CI: 0.0015 to 0.0030; $p < 0.0001$). For cardiac deaths, increasing NT-proBNP levels had a distinctively greater impact on outcomes than the CHA_2DS_2VASc score groups (Fig. 4B). The C-statistic increased from 0.592 (95% CI: 0.568 to 0.617) to 0.691 (95% CI: 0.669 to 0.714) ($p < 0.0001$), with a relative IDI improvement of 270% (IDI: 0.0142; 95% CI: 0.0119 to 0.0165; $p < 0.0001$) compared with the CHA_2DS_2VASc alone. The findings concerning the composite ischemic event endpoint (ischemic stroke, systemic embolism, myocardial infarction, and cardiac death) were very similar. The C-statistic increased from 0.598 (95% CI: 0.579 to 0.617) to 0.660 (95% CI: 0.641 to 0.678) ($p < 0.0001$), with a relative IDI improvement of 162% (IDI: 0.0119; 95% CI: 0.0099 to 0.0139; $p < 0.0001$). In addition to IDI, a category-free (continuous) NRI analysis was performed (Table 2). The continuous NRI was 0.289

Outcome NT-proBNP level (ng/L)	Number of Pts	Apixaban Events (%/year)	Warfarin	HR (95%CI)	p-value for interaction
Stroke/Systemic embolism					0.9636
≤363	3725	23 (0.63)	31 (0.86)	0.74 (0.43-1.27)	
364 - 713	3721	40 (1.10)	44 (1.22)	0.89 (0.58-1.37)	
714 - 1250	3724	50 (1.43)	62 (1.72)	0.83 (0.57-1.20)	
>1250	3722	68 (2.00)	79 (2.43)	0.82 (0.59-1.14)	
Ischemic or unspecified stroke					0.9236
≤363	3725	18 (0.50)	17 (0.47)	1.06 (0.55-2.05)	
364 - 713	3721	31 (0.85)	33 (0.92)	0.92 (0.57-1.51)	
714 - 1250	3724	39 (1.11)	40 (1.11)	1.00 (0.65-1.56)	
>1250	3722	48 (1.41)	54 (1.65)	0.85 (0.57-1.25)	
Hemorrhagic stroke					0.7104
≤363	3725	6 (0.16)	14 (0.38)	0.43 (0.17-1.12)	
364 - 713	3721	9 (0.24)	11 (0.30)	0.80 (0.33-1.94)	
714 - 1250	3724	8 (0.23)	18 (0.49)	0.46 (0.20-1.05)	
>1250	3722	14 (0.41)	20 (0.61)	0.67 (0.34-1.32)	
Death					0.5565
≤363	3725	64 (1.73)	75 (2.02)	0.86 (0.61-1.20)	
364 - 713	3721	82 (2.20)	75 (2.05)	1.08 (0.79-1.47)	
714 - 1250	3724	105 (2.93)	133 (3.60)	0.81 (0.63-1.05)	
>1250	3722	264 (7.52)	270 (8.07)	0.93 (0.79-1.11)	
Cardiac death					0.5842
≤363	3725	30 (0.81)	34 (0.92)	0.89 (0.54-1.45)	
364 - 713	3721	40 (1.07)	33 (0.90)	1.19 (0.75-1.89)	
714 - 1250	3724	56 (1.56)	66 (1.79)	0.87 (0.61-1.25)	
>1250	3722	132 (3.76)	152 (4.54)	0.83 (0.66-1.05)	
Myocardial infarction					0.7922
≤363	3725	10 (0.28)	16 (0.44)	0.63 (0.28-1.38)	
364 - 713	3721	15 (0.41)	14 (0.39)	1.05 (0.51-2.18)	
714 - 1250	3724	17 (0.48)	19 (0.52)	0.92 (0.48-1.77)	
>1250	3722	29 (0.84)	29 (0.89)	0.96 (0.57-1.60)	
Stroke/Systemic embolism/Death					0.7820
≤363	3725	81 (2.23)	95 (2.62)	0.85 (0.63-1.15)	
364 - 713	3721	109 (2.98)	110 (3.06)	0.97 (0.75-1.27)	
714 - 1250	3724	146 (4.16)	178 (4.93)	0.84 (0.68-1.05)	
>1250	3722	305 (8.94)	310 (9.52)	0.94 (0.80-1.10)	
Ischemic stroke/Systemic embolism/Myocardial infarction/Cardiac death					0.7715
≤363	3725	58 (1.60)	61 (1.68)	0.95 (0.66-1.36)	
364 - 713	3721	77 (2.11)	71 (1.99)	1.06 (0.77-1.47)	
714 - 1250	3724	103 (2.95)	120 (3.34)	0.88 (0.68-1.15)	
>1250	3722	188 (5.54)	205 (6.32)	0.88 (0.72-1.07)	
Major bleed					0.2934
≤363	3716	50 (1.49)	76 (2.31)	0.64 (0.45-0.92)	
364 - 713	3714	61 (1.82)	74 (2.24)	0.81 (0.58-1.14)	
714 - 1250	3715	73 (2.24)	130 (3.96)	0.57 (0.43-0.76)	
>1250	3716	96 (3.16)	112 (4.00)	0.79 (0.60-1.04)	

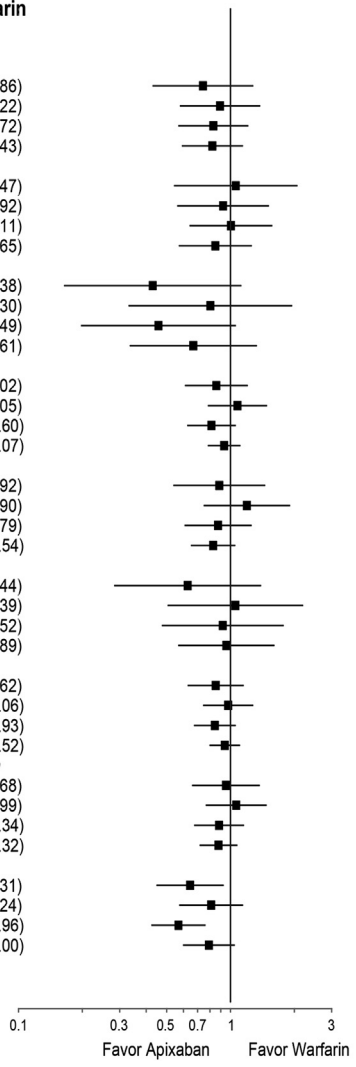

Figure 2 **Efficacy of Apixaban Relative Warfarin for Quartiles of NT-proBNP Level at Baseline**

Cox proportional hazards model with biomarker level, treatment, and interaction between treatment and biomarker level as covariates. Abbreviations as in Figure 1.

(95% CI: 0.195 to 0.384, $p < 0.0001$) for stroke or systemic embolism with events contributing 0.315 and nonevents −0.025. For vascular death, the continuous NRI was 0.508 (95% CI: 0.423 to 0.593, $p < 0.0001$) with events contributing 0.112 and nonevents 0.396. For stroke or systemic embolism, the improved reclassification was among patients experiencing events, whereas for cardiovascular death, the improvement was highest for nonevent patients.

Discussion

The major findings of this study were that NT-proBNP levels are elevated in three-fourths of patients with AF and at least 1 risk factor for stroke. The NT-proBNP concentration was related to age, sex, and comorbidity, as expected, and most strongly to the type of AF, with higher levels in patients with persistent/permanent AF compared with paroxysmal AF. The NT-proBNP level was independently and gradually related to the risk of stroke or systemic embolism and all-cause and cardiac mortality. This predictive value of NT-proBNP was incremental to the CHA_2DS_2VASc score and persisted after adjustment for established risk factors including the CHA_2DS_2VASc score and indicators of renal function and troponin. There was no interaction between NT-proBNP and treatment (i.e., apixaban was superior to warfarin in terms of both efficacy and safety across NT-proBNP quartiles).

The prognostic value of natriuretic peptides is established in elderly subjects living in the community and in patients with stable coronary artery disease, acute coronary

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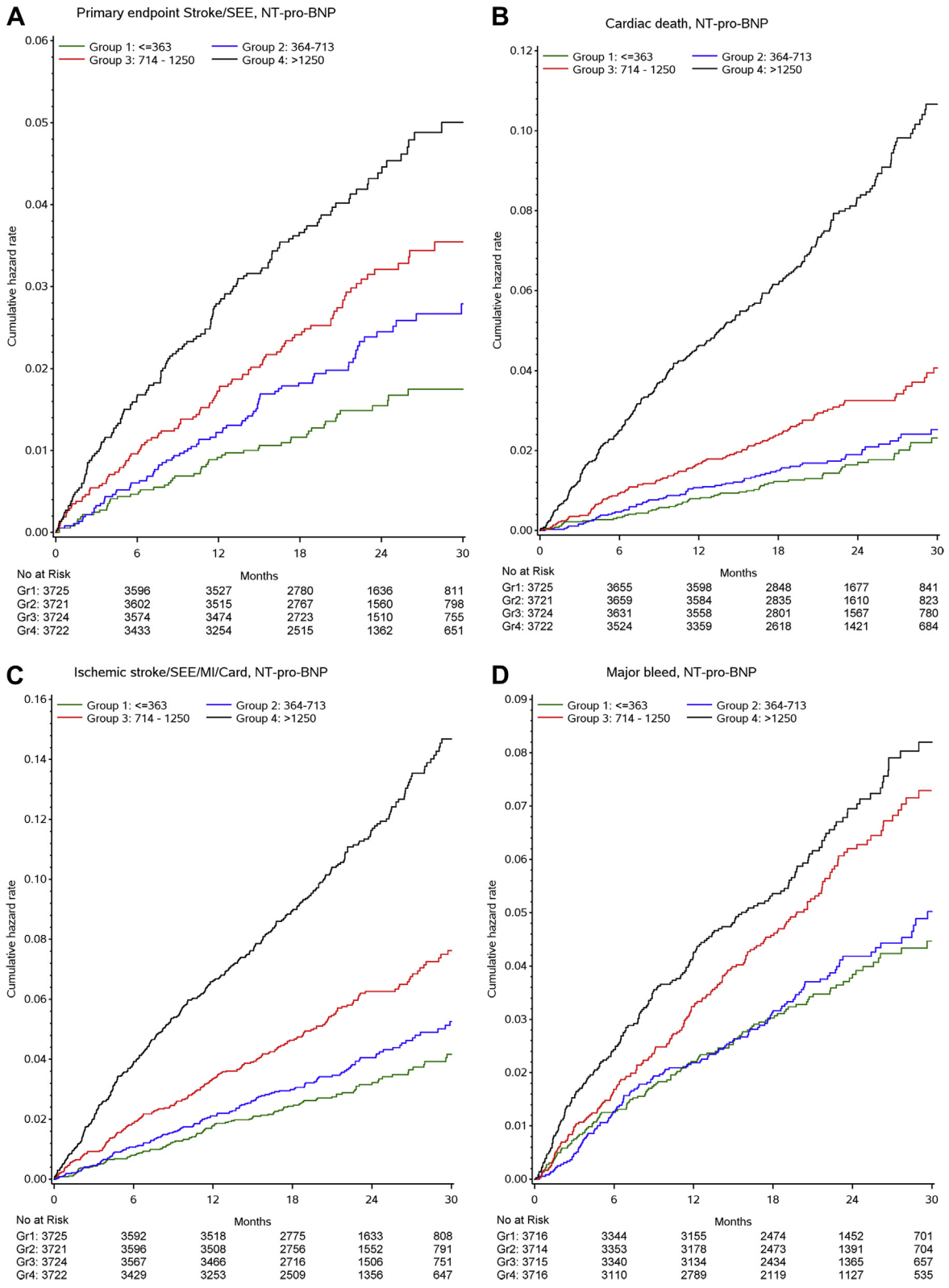

Figure 3 **Cumulative Hazard Rates for Study Endpoints by Quartiles of NT-proBNP**

Cumulative hazard rates for stroke or systemic embolism **(A)**; cardiac death **(B)**; composite of stroke, systemic embolism (SEE), myocardial infarction (MI), and death **(C)**; and major bleeding **(D)**. NT-proBNP = N-terminal pro–B-type natriuretic peptide.

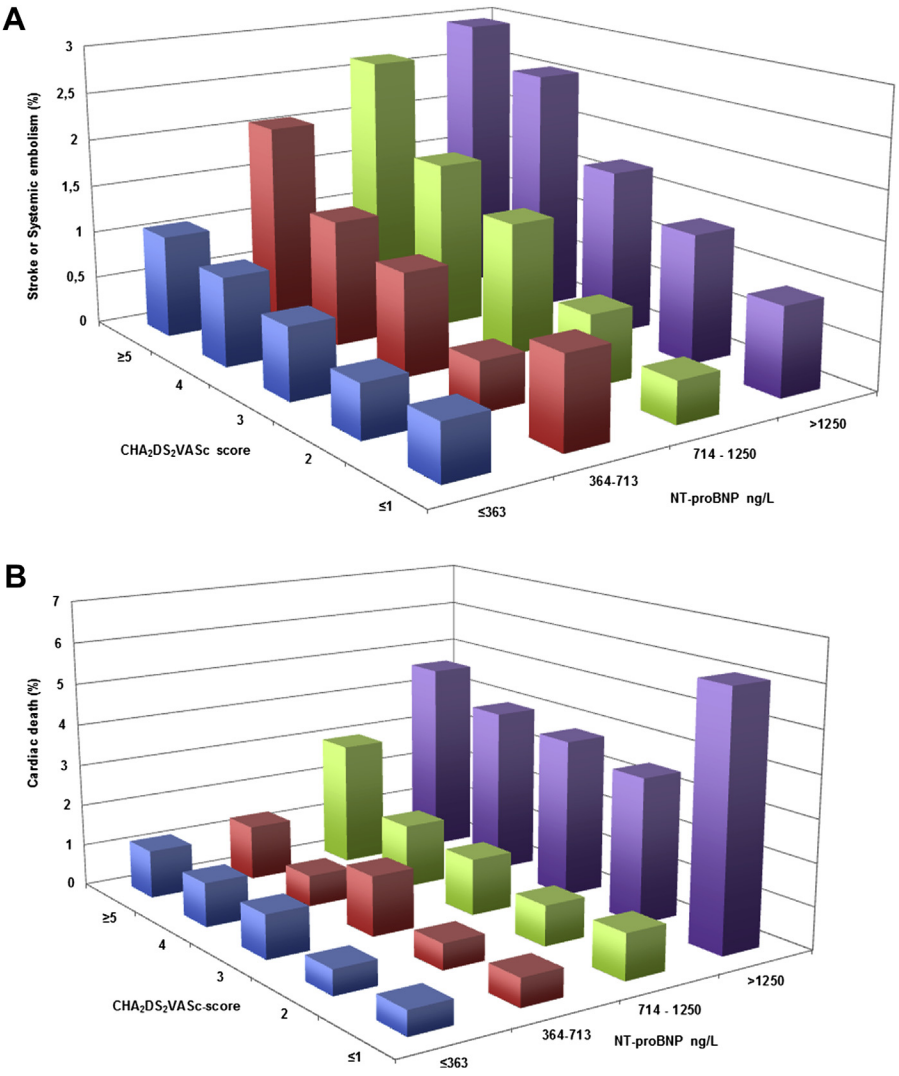

Figure 4 **Study Endpoint in Relation to NT-proBNP Levels and CHA_2DS_2VASc Score**

Stroke and systemic embolism **(A)** and cardiac death **(B)** in relation to N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels and CHA_2DS_2VASc score.

syndromes, and heart failure (10,12–15). Our study extends these findings to subjects with AF and is consistent with the recent findings of the RE-LY trial (11). However, because there were considerably more patients in the present ARISTOTLE biomarker cohort (N = 14,892) compared with RE-LY (N = 6,189), we were able to demonstrate the independent incremental value of adding NT-proBNP to a recommended risk score (CHA_2DS_2VASc score) in relation to individual endpoints (e.g., subtypes of stroke including intracranial bleeding). Despite adjustment for established risk factors including CHA_2DS_2VASc score and biomarkers reflecting different pathways of the renal function (cystatin-C) and myocardial state (high-sensitivity troponin T), the improved risk stratification obtained with NT-proBNP remained highly significant, including more than a doubled risk of stroke and cardiac death (Fig. 1). Further, a consistent risk over the duration of the trial was seen in the NT-proBNP quartiles, allowing the identification of a greater absolute benefit with apixaban compared with warfarin treatment at higher NT-proBNP levels (Fig. 2).

In clinical practice, risk stratification in AF patients is commonly based on clinical risk scores, such as the established CHA_2DS_2VASc risk score, which is derived from clinical variables such as the presence of congestive heart failure, hypertension, age 75 years and older, diabetes, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, and sex category. The present study demonstrated the independent predictive value of NT-proBNP in addition to clinical risk stratification with the CHA_2DS_2VASc score for improving the prognostic discrimination of risk of stroke or systemic embolism and

Table 2 Category-Free Net Reclassification Improvement

Outcome	n	Reclassification Up	Reclassification Down	NRI	NRI Total (95% CI)	p Value
Stroke/systemic embolism						
Event subjects	397	261	136	0.315	0.289 (0.195–0.384)	<0.0001
Nonevent subjects	14,495	7,432	7,063	−0.025		
Cardiac death						
Event subjects	543	302	241	0.112	0.508 (0.423–0.593)	<0.0001
Nonevent subjects	14,349	4,336	10,013	0.396		

CI = confidence interval; NRI = net reclassification improvement.

cardiac death. The C-statistics improved substantially from 0.62 to 0.65 and 0.59 to 0.69 regarding stroke and cardiac death events, respectively. For stroke or systemic embolism events, the NT-proBNP levels and the CHA_2DS_2VASc score distinctively provided complementary information, as illustrated in Figure 4A. The lowest risk was seen in patients with no or minimal elevated levels of NT-proBNP (≤363 ng/l) and a low CHA_2DS_2VASc score (≤2). Despite a CHA_2DS_2VASc score of 0 to 1, if the NT-proBNP level was >1,250 ng/l, the annual risk of stroke and systemic embolism equaled those with a score of ≥3 and levels ≤363 ng/l (Fig. 4A). Concerning cardiac death, mainly NT-proBNP level, but not the CHA_2DS_2VASc score, provided prognostic information, as visually illustrated in Figure 4B, and with 270% improvement according to relative IDI. For both outcomes, a substantial proportion of patients were appropriately reclassified to higher or lower risks as displayed with the category free NRI analysis.

The effect of study treatment in relation to NT-proBNP levels was also analyzed in this study. NT-proBNP is an established sensitive marker for heart failure (6). Heart failure is a well-known risk factor for thromboembolism in AF as well as an independent marker for increased bleeding risk (4,22). We therefore analyzed the effect of the study treatment in relation to NT-proBNP levels and cardiovascular events including major bleeding. Despite the significant increased risk and predictive effect concerning stroke or systemic embolism and mortality with increasing NT-proBNP levels, there was no study treatment interaction with regard to outcomes, thus displaying the superior effect of apixaban over warfarin in terms of both efficacy and safety across NT-proBNP quartiles.

The clinical characteristics included in the CHA_2DS_2VASc risk score have been identified primarily to provide information on stroke but not on other adverse events in AF patients. Accordingly, also in relation to the composite ischemic event endpoint, increasing NT-proBNP levels were more strongly associated with outcomes than the CHA_2DS_2VASc score, and the C-statistic increased from 0.60 to 0.66 ($p < 0.0001$). AF is a well-described risk factor of increased mortality (1). Despite this evidence, in the clinical setting, risk stratification and treatment are mainly focused on primary or secondary stroke prevention. Although in an anticoagulated AF population such as in the RE-LY and ARISTOTLE trial, the total numbers and annual rates of mortality are more than doubled compared with stroke or systemic embolism events (23,24). This study clearly displays the powerful risk prediction gained with NT-proBNP measurements in an AF population concerning mortality, both independently and compared with CHA_2DS_2VASc score. This novel prognostic information may be usable for treatment selection to further improve survival in AF patients. The consistent results from 2 very large, systematic and prospective AF trials such as RE-LY (11) and ARISTOTLE, together including 21,081 patients, enable definite conclusions of the incremental prognostic value of NT-proBNP level for stroke, cardiac, total death, and other ischemic events in patients with AF.

Several of the clinical variables used to assess ischemic stroke risk in AF patients are also used to stratify the risk of major bleeding events, of which the most devastating and feared are the intracerebral hemorrhages (25). Due to the large cohort size in the present study, we are, for the first time, able to discriminate and analyze subtypes of ischemic or hemorrhagic stroke with regard to NT-proBNP levels. The results clearly display a significant elevated risk of ischemic stroke with increasing NT-proBNP level (Fig. 1). These novel findings add important information for the use of NT-proBNP measurements for risk stratification in stable AF patients with regard to competing risks and thromboembolic events.

In the present study, more than three-fourths of the patients had NT-proBNP levels above the upper reference limit for elderly individuals (17). AF rhythm rather than sinus rhythm at the time of blood sampling was most strongly associated with higher NT-proBNP levels, with a >3-fold higher geometric mean. Persistent or permanent compared with paroxysmal AF, older age, lower creatinine clearance, and clinical history of coronary artery disease and heart failure were also associated with higher NT-proBNP levels in this AF cohort, which affirms the results of some previously published small studies (26). Elevated natriuretic peptides reflect the myocyte response to increased wall tension. In AF, levels of natriuretic peptides are elevated compared with matched controls in sinus rhythm in various settings (26–28) and decrease rapidly after restoration of sinus rhythm (29–32). In contrast to the pathophysiology of heart failure in which NT-proBNP is derived mainly from the ventricles, there is support for NT-proBNP release from the atrium in patients with AF as a response to atrial stretch

(33–35). Accordingly, elevated NT-proBNP levels in AF may partly originate from atrial dysfunction, an established marker associated with the formation of atrial thrombi (36), and thereby provide a plausible mechanism for the prognostic importance of elevated NT-proBNP levels and thromboembolic events as presented in this ARISTOTLE biomarker study.

Study limitations. The present findings are derived from a clinical trial population with AF and at least 1 risk factor for stroke and may therefore not be immediately extrapolated to the general AF population. The study design does not permit final conclusions about the optimal cutoff value of NT-proBNP as a decisive tool to select patients for different antithrombotic strategies because all study participants received oral anticoagulants.

Conclusions

The NT-proBNP level is elevated in the majority of patients with persistent or permanent AF. The degree of NT-proBNP elevation has a strong independent association with the risk of stroke and mortality. The relative benefits of apixaban compared with warfarin are consistent, regardless of the NT-proBNP levels, and accordingly the absolute benefits of apixaban will be greater in patients with AF and higher NT-proBNP levels. NT-proBNP might therefore be a novel tool for the selection of patients with AF both for anticoagulation and other treatments.

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