

High-Sensitivity Troponin I for Risk Assessment in Patients With Atrial Fibrillation

Insights From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial

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Background—High-sensitivity troponin-I (hs-TnI) measurement improves risk assessment for cardiovascular events in many clinical settings, but the added value in atrial fibrillation patients has not been described.

Methods and Results—At randomization, hs-TnI was analyzed in 14821 atrial fibrillation patients in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial comparing apixaban with warfarin. The associations between hs-TnI concentrations and clinical outcomes were evaluated by using adjusted Cox analysis. The hs-TnI assay detected troponin (≥ 1.3 ng/L) in 98.5% patients, 50% had levels >5.4 , 25% had levels >10.1 , and 9.2% had levels ≥ 23 ng/L (the 99th percentile in healthy individuals). During a median of 1.9 years follow-up, annual rates of stroke or systemic embolism ranged from 0.76% in the lowest hs-TnI quartile to 2.26% in the highest quartile (>10.1 ng/L). In multivariable analysis, hs-TnI was significantly associated with stroke or systemic embolism, adjusted hazard ratio 1.98 (1.42–2.78), $P=0.0007$. hs-TnI was also significantly associated with cardiac death; annual rates ranged from 0.40% to 4.24%, hazard ratio 4.52 (3.05–6.70), $P<0.0001$, in the corresponding groups, and for major bleeding hazard ratio 1.44 (1.11–1.86), $P=0.0250$. Adding hs-TnI levels to the CHA₂DS₂VASc score improved c-statistics from 0.629 to 0.653 for stroke or systemic embolism, and from 0.591 to 0.731 for cardiac death. There were no significant interactions with study treatment.

Conclusions—Troponin-I is detected in 98.5% and elevated in 9.2% of atrial fibrillation patients. The hs-TnI level is independently associated with a raised risk of stroke, cardiac death, and major bleeding and improves risk stratification beyond the CHA₂DS₂VASc score. The benefits of apixaban in comparison with warfarin are consistent regardless of hs-TnI levels.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00412984.

(*Circulation*. 2014;129:625-634.)

Key Words: atrial fibrillation ■ biological markers ■ cardiovascular diseases ■ risk assessment ■ troponin.

Atrial fibrillation (AF) constitutes a major risk factor for stroke and death.^{1,2} At present, the risk for stroke and the indication for anticoagulant treatment in AF can be estimated

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by clinical risk factors, eg, the CHADS₂ or the later developed CHA₂DS₂VASc score (which assigns 1 point each for a history of congestive heart failure, hypertension, diabetes mellitus, vascular disease, age ≥ 65 years, and sex category [female sex], and 2 points for age ≥ 75 years and previous stroke/

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Received April 26, 2013; accepted October 30, 2013.

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Guest Editor for this article was Ralph L. Sacco, MD.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.113.006286

transient ischemic attack).³ Recently, cardiac troponin, a sensitive indicator of myocardial damage,^{4,5} was identified as an independent marker of increased risk of stroke, other cardiovascular events, and mortality in patients with AF by the use of contemporary assays.⁶ The availability of the next generation of high-sensitivity (hs) troponin assays, which enables the detection of very low troponin concentrations with high precision, has improved the prognostication substantially in several patient populations, such as acute coronary syndromes, congestive heart failure, stable atherosclerotic disease, and even in apparently healthy elderly subjects.^{7–14} Knowledge regarding the prognostic information gained by high-sensitivity troponin assays concerning stroke risk and other cardiovascular events in AF is limited. In this biomarker substudy, we assessed the associations between high-sensitivity troponin I (hs-TnI) concentrations at baseline and clinical outcomes after adjusting for established cardiovascular risk factors in 14821 patients of 18201 within the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.^{15,16} We also compared the prognostic information with that of the CHA₂DS₂VASc score and evaluated the outcomes with apixaban in comparison with warfarin in relation to levels of hs-TnI.

Methods

The ARISTOTLE Trial

The details of the ARISTOTLE trial have been published previously.¹⁶ In brief, ARISTOTLE was a double-blind, double-dummy, randomized clinical trial that enrolled 18201 patients with AF and at least 1 CHADS₂ risk factor for stroke or systemic embolism. Patients were randomly assigned to warfarin (n=9081) or apixaban (n=9120). The primary end point was stroke or systemic embolism. Bleeding was classified according to the International Society on Thrombosis and Haemostasis criteria. The present biomarker cohort consisted of the first 14821 included patients with hs-TnI available. The ARISTOTLE trial was event driven; participants included in the trial after the extension amendment were not included in the prespecified biomarker study. The median length of follow-up was 1.9 years for the participants with hs-TnI available. Approval by the appropriate ethics committees was obtained at all sites. All patients provided written informed consent.

End Points and Clinical Risk Classification

The end points in this study 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); International Society on Thrombosis and Haemostasis major bleeding; composites included stroke or systemic embolism, total death or cardiac death, and myocardial infarction. A blinded clinical events committee using prespecified criteria adjudicated all end points.¹⁶ CHADS₂ and CHA₂DS₂VASc scores were calculated for each patient based on the sum of the corresponding risk factors present at randomization. Patients were classified by CHADS₂ 0 to 1, 2, or ≥3 and by CHA₂DS₂VASc scores according to 0 to 1, 2, 3, 4, and ≥5. Also major bleeding outcomes were evaluated in relation to the HAS-BLED score classified by 0 to 1, 2, or ≥3.

Biochemical Methods

All patients were required to provide plasma samples at randomization that were frozen in aliquots and stored at –70°C until analyzed centrally. The hs-TnI levels were determined with sandwich immunoassays on the ARCHITECT i1000SR (Abbott Diagnostics) according to the instructions of the manufacturer. With this assay the analytic

range is 0.0 to 50000 ng/L; the limit of detection in the UCR laboratory is 1.3 ng/L. The lowest concentration measurable with a coefficient of variation of <20% is 1.6 ng/L, and lowest concentration measurable with a coefficient of variation of <10% is 3.3 ng/L; the 99th percentile upper reference limit for healthy subjects is 23 ng/L.¹⁷

Statistical Analyses

These analyses included the 14821 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 by using frequencies for categorical variables and median and 25th and 75th percentiles for continuous variables. For tests of differences among groups, the χ^2 test was used for categorical variables, and the Kruskal-Wallis test was used for continuous variables.

Multivariable analysis of variance with natural logarithms of hs-TnI as response variable 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 randomly assigned patients and included all events from randomization until the efficacy cutoff date (predefined as January 30, 2011). On-treatment analysis produced results very similar to the intention-to-treat results reported. Bleeding analyses were on treatment, including all randomly assigned 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 incidences of the different end points were summarized in relation to randomized treatment, quartiles of the hs-TnI levels, and CHA₂DS₂VASc and HAS-BLED scores as outlined above.

The outcome in relation to treatment and hs-TnI group were analyzed by using a Cox proportional hazards model including treatment group, hs-TnI quartile group, and treatment by hs-TnI interaction as covariates. The estimated hazard ratios (HRs) were used to assess the treatment effect within each of the subgroups, and the significances of the biomarker interacting with the effect of treatment were judged by the significance of the interaction statistic. The outcomes in relation to hs-TnI quartiles were evaluated both in a simple and in a multivariable Cox proportional hazards model. The multivariable analyses included established risk factors (age [continuous], sex, body mass index, smoking status, systolic blood pressure, heart rate, AF type, diabetes mellitus, history of symptomatic congestive heart failure, previous stroke/systemic embolism/transient ischemic attack, hypertension, previous myocardial infarction, previous peripheral artery disease/coronary artery bypass grafting/percutaneous coronary intervention, treatment at randomization with aspirin, angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker, Amiodarone, for the major bleeding end point; history of anemia and history 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, and biomarkers (cystatin C [a marker of renal function] and N-terminal probrain natriuretic peptide, continuous). In addition, a model including randomized treatment and CHA₂DS₂VASc score as covariates was analysed. The hazard ratios and 95% confidence intervals, with the use of the group with the lowest hs-TnI levels as reference, were reported. The assumption of proportional hazards was assessed visually by log-cumulative hazard plots. We performed likelihood ratio tests to evaluate whether the global model fit improved after the addition of hs-TnI.

The increased discriminative value of hs-TnI was investigated by estimating the c-statistics generalized for survival data¹⁸ for models with and without biomarker and also the continuous (category-free) net reclassification improvement index for survival data as described by Pencina et al.¹⁹ The net reclassification improvement index among events and among nonevents, and the total net reclassification improvement index, as well, were analyzed.

Kaplan–Meier estimates of the cumulative hazard rate were calculated and plotted. All presented event rates were reported per

100 patient-years of follow up. All statistical tests were 2-tailed and performed at the 0.05 significance level. There were no adjustments for multiple comparisons. The Statistics section at Uppsala Clinical Research Center conducted the statistical analyses. All statistical analyses were performed using SAS software, version 9.3 (SAS institute Inc, Cary, NC).

Results

Distribution of hs-TnI

hs-TnI was detectable in 98.46% (14 593) of the patients. The hs-TnI distribution showed the following levels: mean, 15.7; median, 5.4 (25th percentile 3.3, 75th percentile 10.1) ng/L in the total population without any differences between the randomized treatment groups. Accordingly, $\approx 25\%$ had hs-TnI levels equal to or below the 10% coefficient of variation concentration (3.3 ng/L), 50% had hs-TnI levels >5.4 ng/L, and 25% had hs-TnI levels >10.1 ng/L. A total of 9.2% was considered to have elevated levels based on the 99th percentile limit of a healthy population (23 ng/L).

Baseline Characteristics

Baseline characteristics and medications according to quartiles of hs-TnI are shown in the Table. The majority of risk factors that constitute the CHADS₂ and CHA₂DS₂VASc scores were more common in patients with higher hs-TnI levels. Accordingly, the accumulated score for both the CHADS₂ and CHA₂DS₂VASc models increased with rising hs-TnI, 79.2% of patients with hs-TnI >10 ng/L had CHA₂DS₂VASc >2 in contrast to only 58.4% of patients with hs-TnI ≤ 3.3 ng/L. In multivariable analysis renal impairment, congestive heart failure, male sex, previous vascular disease (stroke, peripheral arterial disease, coronary artery disease), permanent or persistent AF, age, diabetes mellitus, and higher body mass index, had the strongest independent relations to the hs-TnI levels ($P < 0.001$ for all).

Relation of hs-TnI to Stroke or Systemic Embolism in AF

There was a total of 397 (1.40%/y) stroke or systemic embolism during the median follow-up of 1.9 years. There was a marked increase in annual rates with rising hs-TnI levels. In unadjusted analysis, there was a 3-fold increase of stroke or systemic embolism in the comparison of patients with hs-TnI ≤ 3.3 ng/L and >10.1 ng/L with annual rates ranging from 0.76% to 2.26%, respectively. The association remained significant in the adjusted Cox analysis which displayed an increased risk with hs-TnI levels >5.4 ng/L (HR, 1.49; 95% confidence interval, 1.06–2.09) and approximately doubled the hazard with hs-TnI >10.1 ng/L (HR, 1.98; 95% confidence interval, 1.42–2.78) (Figure 1).

hs-TnI in Relation to Mortality and Cardiovascular Events

A total of 1075 (3.69%/y) all-cause mortality, 547 (1.88%/y) cardiac deaths, 150 (0.52%/y) myocardial infarctions, and 674 (2.61%/y) major bleedings were observed in this sub-study cohort. Higher hs-TnI levels were strongly and significantly associated with a higher rate of all outcome events

in the adjusted Cox analysis (Figure 1). In regard to cardiac mortality, the risk increased gradually by higher hs-TnI levels reaching an adjusted HR of 4.52 (3.05–6.70) in the group with hs-TnI >10.1 ng/L versus the group with hs-TnI ≤ 3.3 ng/L. Despite the overall low event rates, there was a similar association between hs-TnI levels and subsequent myocardial infarction with a significantly raised risk by higher hs-TnI and adjusted HR 3.42 (1.82–6.42) in the group with hs-TnI >10.1 ng/L versus the group with hs-TnI ≤ 3.3 ng/L. The rates of the composite of the individual events demonstrated correspondingly strong significant associations with increasing hs-TnI levels. Also, the rate of major bleeding displayed a relationship to increased hs-TnI levels, although nongradual, with an adjusted HR 1.44 (1.11–1.86) in the group with the highest versus lowest quartile hs-TnI levels. As illustrated in the Kaplan–Meier plots (Figure 2A through 2C) the associations between hs-troponin levels at baseline and the risk for subsequent events remained stable over time.

There was no significant interaction for any of the outcomes in relation to the randomized treatments with the hs-TnI levels at baseline (Figure 3). Thus, there were consistent reductions in stroke, hemorrhagic stroke, total mortality, composites of these events, and major bleeding consistent with the overall trial irrespective of hs-TnI levels (all interaction P values of >0.40). The randomized treatment groups were therefore combined and adjusted for when the association between hs-TnI levels and the above outcomes in the multivariable analyses were evaluated.

Risk Stratification Using hs-TnI in Comparison With the CHA₂DS₂VASc and HAS-BLED Scores

Annual rates of stroke or systemic embolism according to hs-TnI levels and CHA₂DS₂VASc score are illustrated in Figure 4A. The rates increased with both increasing CHA₂DS₂VASc score and higher hs-TnI level. Within CHA₂DS₂VASc score 0 to 1 the annual rate of stroke or systemic embolism ranged from 0.16% to 2.36% depending on hs-TnI quartiles. Patients with hs-TnI <3.3 ng/L and a CHA₂DS₂VASc score up to 2 had an average annual rate of 0.35%. The groups with the highest rates, 2.14% to 3.48% per year, all had hs-TnI levels >10.1 ng/L. The c-statistic was 0.629 for a model with CHA₂DS₂VASc score alone and 0.612 for a model with hs-TnI alone and increased substantially to 0.653, by adding hs-TnI to the CHA₂DS₂VASc score.

In relation to mortality and cardiovascular events, hs-TnI levels had a substantially larger impact on outcomes in comparison with the CHA₂DS₂VASc score. For cardiac mortality (Figure 2B), increasing hs-TnI level had a stronger association with event rates than the CHA₂DS₂VASc score. A model with CHA₂DS₂VASc score alone yielded a c-statistic of 0.591 for cardiac mortality, a model with hs-TnI alone yielded a c-statistic of 0.719 which increased to 0.731 by adding hs-TnI to the CHA₂DS₂VASc score. Accordingly, also for the composite of ischemic events and mortality, hs-TnI had a better discriminative ability than the CHA₂DS₂VASc score, with c-statistic 0.598 for a model with CHA₂DS₂VASc score alone, 0.675 for a model with hs-TnI alone, and increasing to 0.690 by adding hs-TnI to the CHA₂DS₂VASc score. Regarding major bleeding there was a consistent increase both with increasing

Table. Summary of Demographics and Baseline Characteristics by Groups of hs-TnI Level at Baseline.

	hs-TnI level, ng/L				P Value
	≤3.3	>3.3–5.4	>5.4–10.1	>10.1	
n	3889	3592	3658	3682	
Age, median(Q1, Q3)	66.0 (59.0, 73.0)	70.0 (63.0, 76.0)	72.0 (65.0, 77.0)	71.0 (64.0, 77.0)	<0.0001
Sex male, n (%)	2346 (60.3)	2188 (60.9)	2422 (66.2)	2572 (69.9)	<0.0001
Weight, kg, median (Q1, Q3)	84.0 (71.6, 98.0)	82.0 (70.2, 95.5)	82.0 (70.0, 95.0)	80.0 (68.0, 94.0)	<0.0001
Heart rate	75.0 (66, 85)	76.0 (66, 86)	76.0 (66, 85)	75.0 (65, 85)	0.13
Permanent or persistent AF, n (%)	3059 (78.7)	3023 (84.2)	3221 (88.1)	3271 (88.8)	<0.0001
AF duration ≥ 2 y, n (%)	2024 (52.0)	1960 (54.6)	1964 (53.7)	1940 (52.7)	0.13
NYHA class, n (%)					<0.0001
I	2438 (62.7)	2048 (57.0)	1806 (49.4)	1478 (40.1)	
II	1213 (31.2)	1277 (35.6)	1439 (39.3)	1551 (42.1)	
III	229 (5.9)	257 (7.2)	388 (10.6)	620 (16.8)	
IV	4 (0.1)	4 (0.1)	16 (0.4)	27 (0.7)	
Calculated CrCL, mL/min, median (Q1, Q3)	83.3 (66.2, 106.8)	75.8 (59.3, 95.3)	70.2 (53.5, 90.3)	65.5 (49.3, 86.6)	<0.0001
CHADS ₂ risk factors, n (%)					
CHF or LVEF≤40%	943 (24.2)	1053 (29.3)	1443 (39.4)	1876 (51.0)	<0.0001
Hypertension	3396 (87.3)	3150 (87.7)	3220 (88.0)	3203 (87.0)	0.57
Age ≥ 75 y	743 (19.1)	1079 (30.0)	1384 (37.8)	1343 (36.5)	<0.0001
Diabetes mellitus	892 (22.9)	766 (21.3)	963 (26.3)	1042 (28.3)	<0.0001
Previous stroke or TIA	612 (15.7)	673 (18.7)	729 (19.9)	773 (21.0)	<0.0001
CHA ₂ DS ₂ VASc risk factors, n (%)					
Age 65–74 y	612 (15.7)	673 (18.7)	729 (19.9)	773 (21.0)	<0.0001
Sex female	1543 (39.7)	1404 (39.1)	1236 (33.8)	1110 (30.1)	<0.0001
Myocardial infarction	256 (6.6)	348 (9.7)	571 (15.6)	724 (19.7)	<0.0001
Previous PCI/CABG	436 (11.2)	536 (14.9)	720 (19.7)	812 (22.1)	<0.0001
Peripheral artery disease	106 (2.7)	154 (4.3)	209 (5.7)	253 (6.9)	<0.0001
CHADS ₂ , n (%)					
CHADS ₂ ≤1	1773 (45.6)	1345 (37.4)	1029 (28.1)	879 (23.9)	<0.0001
CHADS ₂ =2	1342 (34.5)	1305 (36.3)	1348 (36.9)	1350 (36.7)	
CHADS ₂ ≥3	774 (19.9)	942 (26.2)	1281 (35.0)	1453 (39.5)	
CHA ₂ DS ₂ VASc, n (%)					
CHA ₂ DS ₂ VASc ≤1	564 (14.5)	296 (8.2)	221 (6.0)	210 (5.7)	<0.0001
CHA ₂ DS ₂ VASc =2	1051 (27.0)	833 (23.2)	639 (17.5)	558 (15.2)	
CHA ₂ DS ₂ VASc =3	1043 (26.8)	952 (26.5)	914 (25.0)	934 (25.4)	
CHA ₂ DS ₂ VASc =4	712 (18.3)	809 (22.5)	889 (24.3)	883 (24.0)	
CHA ₂ DS ₂ VASc ≥5	519 (13.3)	702 (19.5)	995 (27.2)	1097 (29.8)	
Medications at randomization, n (%)					
Aspirin	1132 (29.1)	1035 (28.8)	1181 (32.3)	1232 (33.5)	<0.0001
Warfarin	2199 (56.5)	1979 (55.1)	1954 (53.4)	1838 (49.9)	<0.0001
ACE inhibitor or ARB	2530 (65.1)	2477 (69.0)	2678 (73.2)	2805 (76.2)	<0.0001
Calcium channel blocker	1306 (33.6)	1135 (31.6)	1073 (29.3)	1008 (27.4)	0.0049
β-Blocker	2587 (66.5)	2261 (62.9)	2273 (62.1)	2244 (60.9)	<0.0001
Digoxin	830 (21.3)	1018 (28.3)	1367 (37.4)	1595 (43.3)	<0.0001

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CHF, congestive heart failure; CrCL, creatinine clearance; hs-TnI, high-sensitivity troponin I; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; Q, quartile; and TIA, transient ischemic attack.

hs-TnI and HAS-BLED score groups (Figure 4C). The c-statistic was 0.606 for HAS-BLED score alone, 0.598 for hs-TnI alone, and increased to 0.630 by adding hs-TnI to the HAS-BLED score.

Models that included hs-TnI showed better global fit than models with only CHA₂DS₂VASc or HAS-BLED score and treatment arm, as evaluated by likelihood ratio tests (all

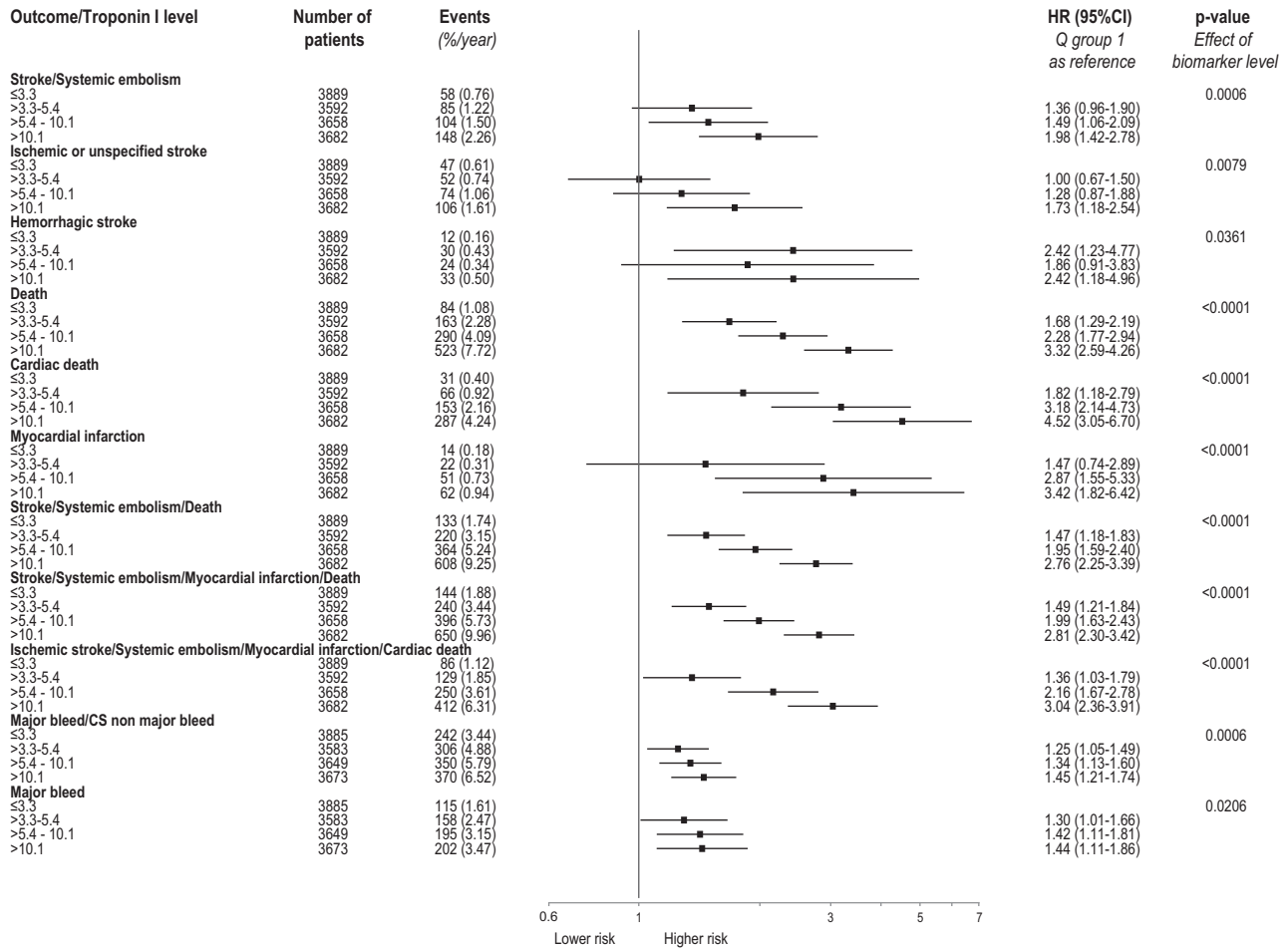


Figure 1. Association between hs-troponin I level at baseline and outcomes. Cox proportional hazards model adjusted for established risk factors (age, sex, body mass index, smoking status, systolic blood pressure, heart rate, AF type, diabetes mellitus, heart failure, previous stroke/systemic embolism/TIA, hypertension, previous myocardial infarction, previous peripheral artery disease/CABG/PCI, treatment at randomization with aspirin, ACE inhibitors or ARB, Amiodarone, for the major bleeding end point; history of anemia and history of spontaneous or clinically 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 NT-proBNP).

$P < 0.0001$). Moreover, the addition of hs-TnI also improved the discrimination in models incorporating all variables used in the adjusted Cox model for all outcomes (results not shown).

The improvement in risk prediction by adding hs-TnI to a model with a CHA₂DS₂VASc score as measured by the continuous net reclassification improvement index (95% confidence interval) was 22% (10%–40%) for stroke or systemic embolism and 63% (54%–72%) for cardiac death. For stroke or systemic embolism events, the amount of correct reclassification was greater among non-event patients (contributing 17%), and, for cardiac death, the amount of correct reclassification was greater among the event patients (contributing 46%).

Discussion

The major findings of this study were that by using high-sensitivity assays troponin I was detectable in 98.5% and elevated in 9.2% of the patients with nonvalvular AF and at least 1 risk factor for stroke. The relation between hs-TnI and stroke or systemic embolic events, cardiac and total death, and myocardial infarction was gradual and remained highly significant

in adjusted analysis. hs-TnI measurements improved risk stratification and risk prediction beyond clinically established models such as the CHA₂DS₂VASc score.

The present results support the independent prognostic value of troponin I levels concerning the risk of stroke, mortality, composite ischemic events, and major bleeding in patients with AF as recently shown from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.⁶ In the RE-LY biomarker study, troponin I was measured in 6189 patients with the use of a contemporary assay (Access AccuTnI assay, Beckman Coulter). High-sensitivity troponin assays enable the detection of even lower levels of troponin I and improvements in the measurement accuracy, as well. By using the Beckman Access AccuTnI assay, 57% of the AF patients in RE-LY were shown to have detectable troponin I, and 8% were classified as having troponin I above the 99th percentile, in comparison with 98.5% with detectable and 9.2% above the 99th percentile with the current Abbott ARCHITECT hs-TnI assay in the present study. The considerably larger number of patients (n=14 821) and the more sensitive troponin assay in the present study in comparison with

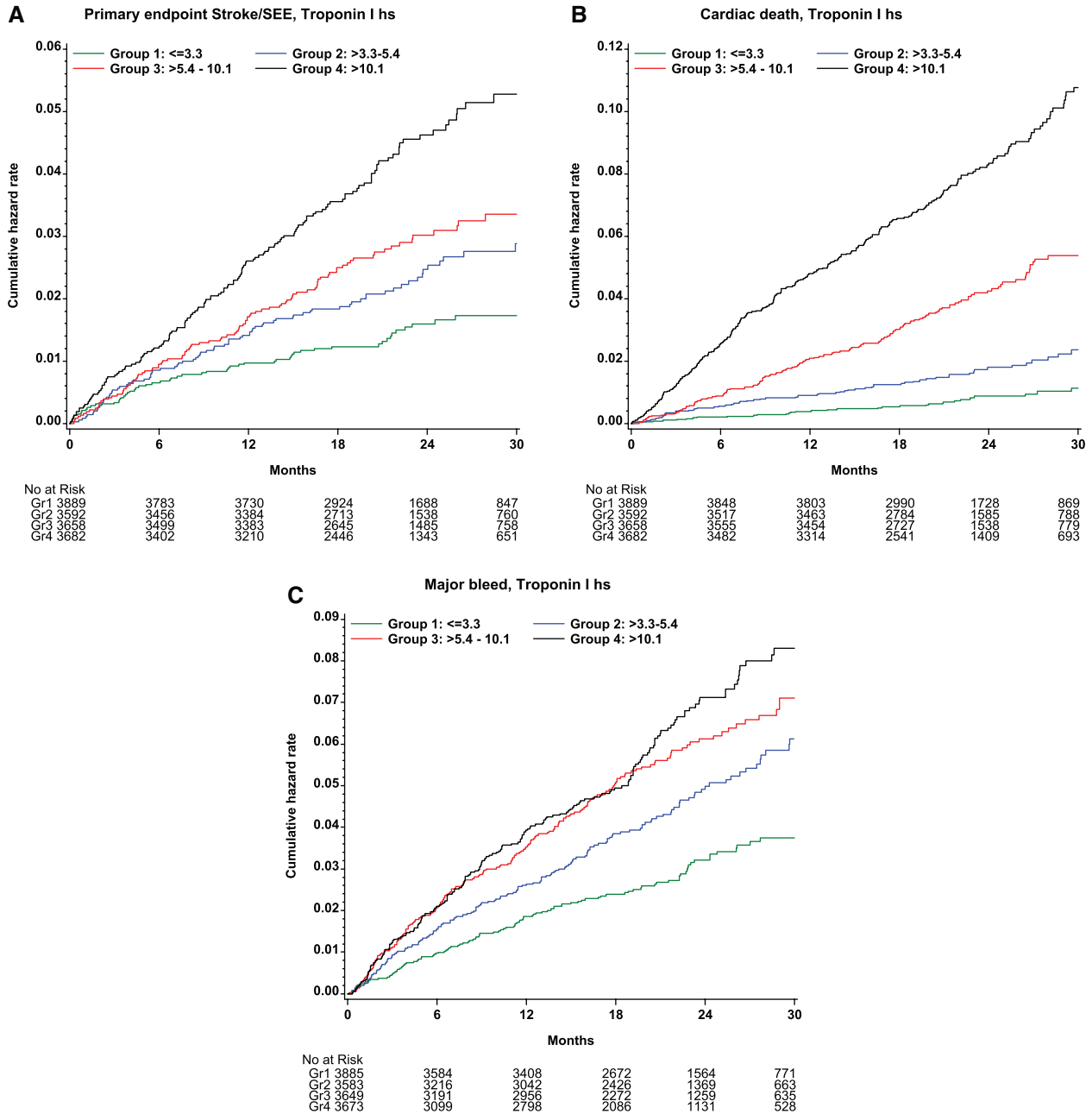


Figure 2. Cumulative hazard rate for the primary outcome (stroke or systemic embolism) (A), cardiac death (B), and major bleeding (C) by levels of hs-troponin I level at baseline. hs indicates high sensitivity; and SEE, systemic embolism.

the RE-LY (n=6189) biomarker study demonstrated a greater discriminatory power of the hs-TnI than conventional TnI levels concerning all outcome events. In addition, there was a larger additive value in the comparison and combination with the CHA₂DS₂VASc score. By adding information of hs-TnI to the CHA₂DS₂VASc risk score identification of patients at both lower and higher risk of stroke was improved in comparison with either information alone. A substantially lower risk was displayed in those having both a low hs-TnI level (≤3.3 ng/L) and a low CHA₂DS₂VASc score (≤2). Further, the determination of hs-TnI among patients with a CHA₂DS₂VASc score ≤2 identified patients with annual rates of stroke similar to patients with CHA₂DS₂VASc scores ≥3. The hs-TnI information therefore adds clinically important information allowing

identification of patients that, despite low CHA₂DS₂VASc scores, still are at high risk of stroke. Consequently, the addition of hs-TnI to the clinical information should improve therapeutic decision making concerning the need for oral anti-coagulation in patients with AF.

The clinical characteristics included in the CHA₂DS₂VASc risk score have been based on their relations to the risk of stroke but not to the risk of other adverse events in AF patients. This study clearly showed that, concerning other outcomes such as cardiac mortality and myocardial infarction, hs-TnI levels alone provided better prognostic information than the CHA₂DS₂VASc risk score. AF is a well-established risk factor not only for stroke, but also for increased mortality.¹ So far, risk stratification and selection of treatment in AF is mainly

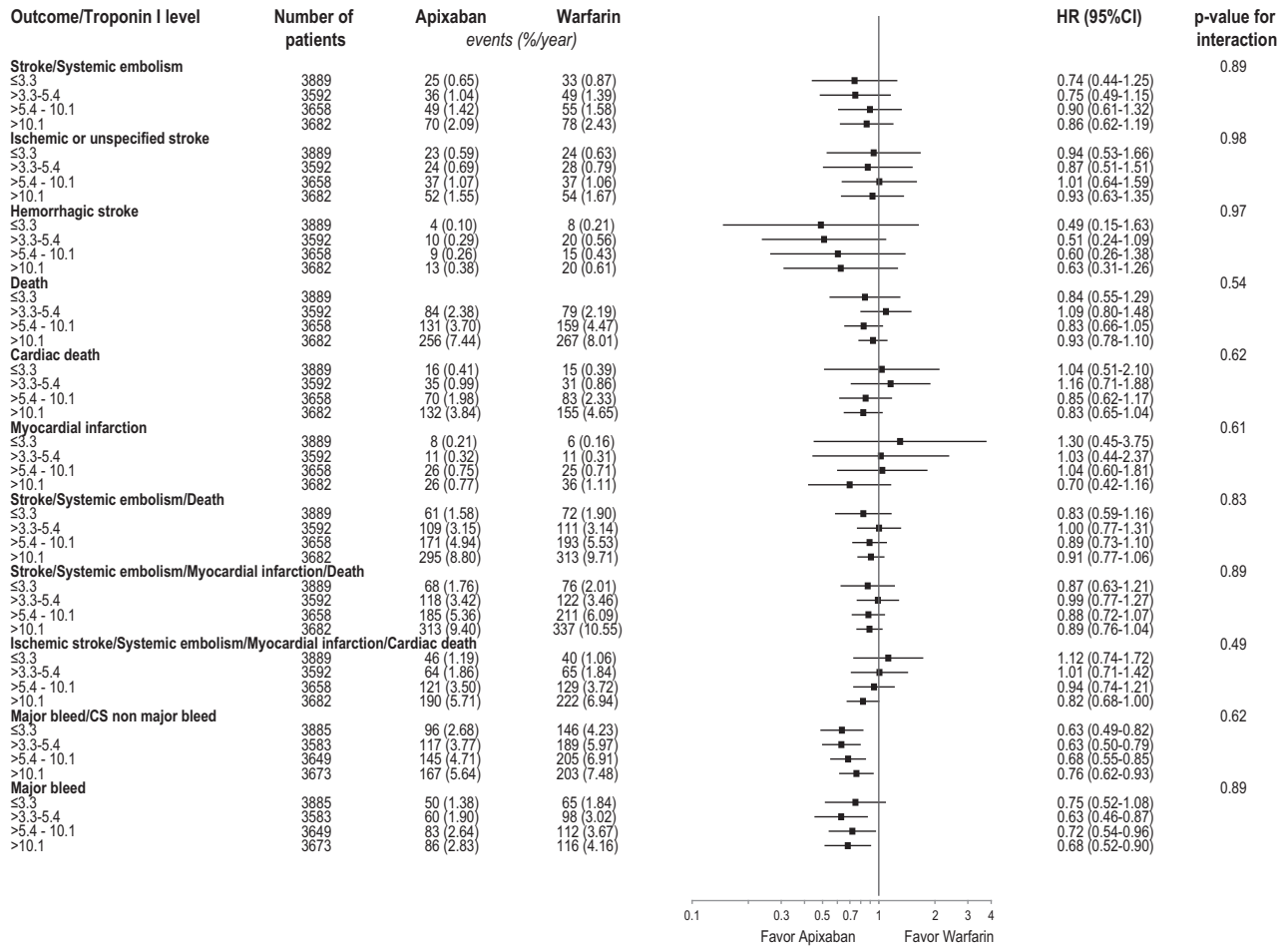


Figure 3. Efficacy of apixaban relative warfarin in relation to hs-troponin I level at baseline. Cox proportional hazards model with biomarker level, treatment, and interaction between treatment and biomarker level as covariates. CI indicates confidence interval; HR, hazard ratio; and hs, high sensitivity.

focused on primary or secondary stroke prevention. However, in an anticoagulated AF population, such as in the RE-LY and ARISTOTLE trial, the total numbers and annual rates of death are more than double as common as events of stroke or systemic embolism.^{15,20} Our study clearly demonstrated the powerful risk prediction obtained with hs-TnI measurements in an AF population concerning mortality, both independently and in comparison with CHA₂DS₂VASc. Accordingly hs-TnI provides a novel tool for identification of AF patients at increased risk of both stroke and death and may therefore be useful for selecting patients not only for anticoagulation, but also for other treatment measures to improve survival in AF patients.

Cardiac troponin is established as a sensitive indicator of myocardial damage.^{4,5} By using hs assays, even very low levels of cardiac troponin become measurable. This has led to substantial improvements in the detection of the marker and also in regard to risk stratification in patients with acute and chronic coronary diseases, in patients with congestive heart failure, and even in healthy elderly subjects.^{7,8,10-13} The underlying mechanisms for this independent relationship are probably multifactorial because the level of hs-troponin is related to aging and tissue vulnerability, myocardial necrosis and apoptosis, myocardial stress, eg, due to increased

or variable heart rates, myocardial dysfunction with variations in atrial and ventricular volume and pressure load, and potential episodes of myocardial ischemia.²¹⁻²⁵ The detection of cardiac troponin in serum in patients with stable coronary artery disease or even apparently healthy individuals have contributed to the proposals of alternative mechanisms for low-level troponin release in contrast to myocyte necrosis as seen in acute coronary syndromes. Mechanisms such as increased physiological myocyte turnover, cellular release, and reversible increase in cell wall permeability to cardiac troponins or troponin fragments have been proposed.^{26,27} In the setting of AF, there may also be an association with underlying inflammatory and fibrotic processes, including endothelial dysfunction contributing to the perpetuation of the arrhythmia, to a hypercoagulable state, and to the risk of thromboembolism.²⁸⁻³¹ However, even without a complete understanding of the underlying mechanisms for elevation of hs-troponin in AF, its incremental information on the risk for cardiovascular events should make it useful for improved risk assessment in AF.

Limitations

The present findings derived from a clinical trial population with AF and at least 1 risk factor for stroke and may therefore

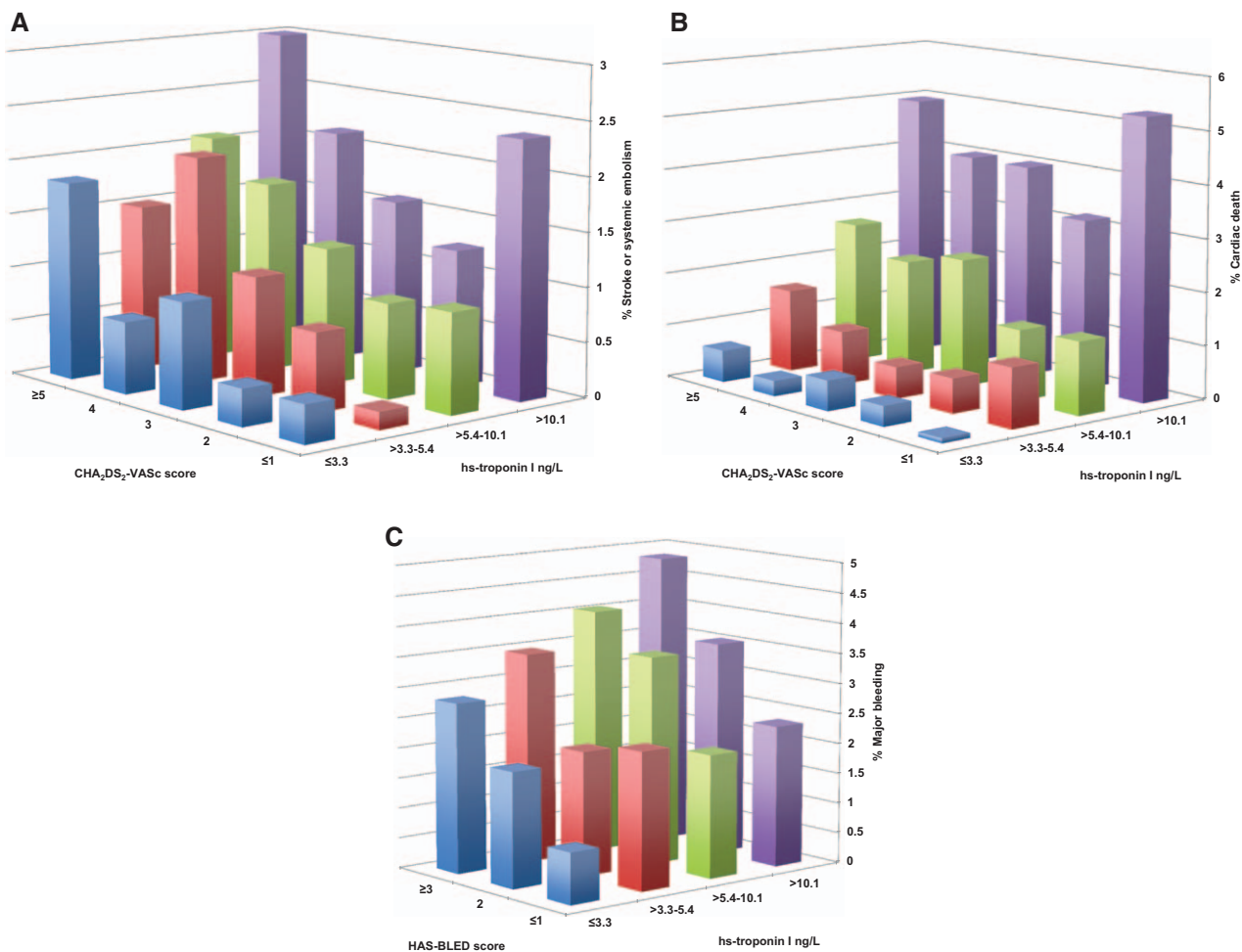


Figure 4. Event rates for stroke and systemic embolism (**A**) and cardiac death (**B**) in relation to levels of hs-troponin I and the CHA₂DS₂-VASc risk score stratified 0 to 1, 2, 3, 4, and ≥ 5 . (Patient numbers in rising hs-troponin I quartiles at CHA₂DS₂-VASc score 0–1 are 625, 325, 205, and 143; at score 2, patient numbers are 1137, 805, 685, and 472; at score 3, patient numbers are 1039, 888, 947, and 994; at score 4, patient numbers are 713, 750, 939, and 898; and at score ≥ 5 , patient numbers are 560, 662, 909, and 1195). **C**, Event rates for major bleeding in relation to levels of hs-troponin I and the HAS-BLED score stratified 0 to 1, 2, and ≥ 3 . (Patient numbers in rising hs-troponin I quartiles at HAS-BLED score 0–1 are 1725, 1235, 1316, and 1190; at score 2, patient numbers are 1348, 1414, 1395, and 1412; and at score ≥ 3 , patient numbers are 816, 1033, 881, and 1056). hs indicates high sensitivity.

not be immediately extrapolated to the general AF population. The study design does not permit final conclusions about the optimal cutoff value of hs-TnI as a decisive tool to select patients for different antithrombotic strategies, because all study participants received oral anticoagulants.

Conclusion

In patients with AF, hs-TnI is detectable in 98.5% and elevated in 9.2%. The relations between hs-TnI and the risk of stroke, myocardial infarction, cardiac and total death, and major bleeding were both gradual and independent. The addition of hs-TnI to clinical risk stratification models for stroke, such as the CHA₂DS₂-VASc risk score, allows an improved risk assessment and safer identification of patients at very low risk and higher risk not detected with the CHA₂DS₂-VASc score. Concerning cardiac mortality and other ischemic events hs-TnI alone carries more prognostic information than the CHA₂DS₂-VASc score. The benefits of apixaban as compared with warfarin were consistent regardless of the hs-TnI levels.

Acknowledgments

Authors Contribution: Dr Wallentin at Uppsala Clinical Research Center, Drs Granger, Alexander, and Lopes at Duke Clinical Research Institute, and Dr Mohan at Bristol-Myers Squibb designed, led, and contributed to the main ARISTOTLE trial performance, statistical analyses, interpretation and reporting of the main results. An international Steering Committee was responsible for overall trial design and conduct. This additional study was mainly designed and led by Drs Wallentin and Hijazi, who also drafted the first version of the manuscript and take full responsibility for the integrity of the data and the accuracy of the data analyses. Other coauthors contributed to the design and performance of the main trial and as National Leaders of the main trial. All coauthors provided input on interpretation of the data, carefully reviewed manuscript drafts and approved the final version of the manuscript for submission. Ulla Nässander Schikan, PhD, at Uppsala Clinical Research Center, Uppsala, Sweden, provided editorial assistance.

Sources of Funding

The trial was funded by Bristol-Myers Squibb, Co, Princeton, NJ, and Pfizer Inc, New York, NY, and coordinated by the Duke Clinical Research Institute, Durham, NC, and Uppsala Clinical Research

Center (UCR), Sweden. Both academic research institutes and the sponsors had full access to the database. UCR received funding from Bristol-Myers Squibb for the independent statistical analysis performed by Ulrika Andersson.

Disclosures

Dr Hijazi reports lecture fees and an institutional research grant from Boehringer Ingelheim. Dr Siegbahn reports institutional research grants from AstraZeneca, Boehringer Ingelheim and Bristol-Mayer Squibb. Dr Granger reports grants from Boehringer Ingelheim, Bristol Myers Squibb, Glaxo SmithKline, Medtronic Foundation, Merck & Co, Pfizer, Sanofi-Aventis, Takeda, the Medicine's Company; consulting fees from Boehringer Ingelheim, Bristol Myers Squibb, Glaxo SmithKline, Hoffmann-La Roche, Novartis Pharmaceutical Company, Lilly, Pfizer, Sanofi-Aventis, Takeda, the Medicine's Company, AstraZeneca. Dr Alexander reports grants from Bristol-Myers Squibb, Merck/Schering-Plough, and Regado Biosciences; travel support from Bristol-Myers Squibb; consulting fees from Bristol-Myers Squibb, Pfizer, Merck/Schering-Plough, AstraZeneca, Boehringer-Ingelheim, Ortho-McNeil-Janssen Pharmaceuticals, PolyMedix, Regado Biosciences, Bayer, and Daiichi-Sankyo. Dr Atar reports honoraria from Boehringer-Ingelheim, Bristol Myers Squibb, Pfizer, and Nycomed-Takeda. Dr Gersh reports consultancy fees from PPD Development, Cardiovascular Research Foundation, InspireMD, Boston Scientific, Baxter Healthcare Corporation, St. Jude Medical. Dr Mohan was an employee of Bristol-Myers Squibb and received stock as a part of compensation. Dr Harjola reports consulting and lecture fees from Abbott Laboratories, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Novartis, and Orion Pharma. Dr Horowitz reports consulting fees, travel support and Executive Committee Member for Bristol-Myers Squibb; lecture fees from Bristol-Myers Squibb and Pfizer. Dr Husted reports being an advisory board member for AstraZeneca, Bristol-Myers Squibb, Pfizer, and Bayer; research support from GlaxoSmithKline, Pfizer, and Sanofi-Aventis. Dr Hylek reports consulting fees, travel support and Adjudication Committee member for Bristol-Myers Squibb, Daiichi Sankyo, Merck, Ortho-McNeil, Johnson & Johnson, and Pfizer, lecture fees from Boehringer-Ingelheim. Dr Lopes reports grants from Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, DaiichiSankyo and consulting fees from Bristol-Myers Squibb, Pfizer, Bayer, and Janssen Research & Development, L.L.C. Dr McMurray reports research grant from Bristol-Myers Squibb/Pfizer. Dr Wallentin reports research grants from AstraZeneca, Merck & Co, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline; consultant for Merck & Co, Regado Biosciences, Evolva, Portola, C.S.L. Behring, Athera Biotechnologies, Boehringer-Ingelheim, AstraZeneca, GlaxoSmithKline, and Bristol-Myers Squibb/Pfizer; lecture fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and Merck & Co.; honoraria from Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and Merck & Co.; travel support from AstraZeneca and Bristol-Myers Squibb/Pfizer. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Troponin is a widely available biomarker for the diagnosis and prognostication of cardiac diseases. By using high-sensitivity assays, we demonstrated that cardiac troponin I was detectable in almost all (98.5%) patients and elevated in 9.3% of patients with atrial fibrillation. Determination of troponin levels with a high-sensitivity assay provided incremental discriminative information to the currently used CHA₂DS₂-VASc and HAS-BLED risk scores. Beyond clinical risk factors, an elevated level of troponin I identified patients with a doubled risk for stroke or systemic embolism and an up to 4.5-fold increased risk of vascular death. Troponin I measurements improved risk prediction substantially in patients with atrial fibrillation beyond currently used clinical risk scores. The availability of the cardiac troponin analysis is widespread and easily accessible and makes it a very attractive candidate for use to improve the prognostication of patients with atrial fibrillation in addition to the currently recommended clinical risk stratification models.

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High-Sensitivity Troponin I for Risk Assessment in Patients With Atrial Fibrillation: Insights From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial

Ziad Hijazi, Agneta Siegbahn, Ulrika Andersson, Christopher B. Granger, John H. Alexander, Dan Atar, Bernard J. Gersh, Puneet Mohan, Veli-Pekka Harjola, John Horowitz, Steen Husted, Elaine M. Hylek, Renato D. Lopes, John J.V. McMurray and Lars Wallentin
on behalf of the ARISTOTLE Investigators

Circulation. 2014;129:625-634; originally published online November 13, 2013;
doi: 10.1161/CIRCULATIONAHA.113.006286

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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