Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 1, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.07.093

High-Sensitivity Troponin T and Risk Stratification in Patients With Atrial Fibrillation During Treatment With Apixaban or Warfarin

Ziad Hijazi, MD, PhD,*† Lars Wallentin, MD, PhD,*† Agneta Siegbahn, MD, PhD,*‡ Ulrika Andersson, MSc,* John H. Alexander, MD, MHS,§ Dan Atar, MD,‖ Bernard J. Gersh, MB, ChB, DPhil,¶ Michael Hanna, MD,# Veli Pekka Harjola, MD, PhD,** John D. Horowitz, MD, PhD,†† Steen Husted, MD, MSc,‡‡ Elaine M. Hylek, MD, MPH,§§ Renato D. Lopes, MD, PhD,§ John J. V. McMurray, MD,‖‖ Christopher B. Granger, MD,§ on behalf of the ARISTOTLE Investigators

Uppsala, Sweden; Durham, North Carolina; Oslo, Norway; Rochester, Minnesota; Princeton, New Jersey; Helsinki, Finland; Adelaide, South Australia, Australia; Herning/Holstbro, Denmark; Boston, Massachusetts; and Glasgow, Scotland, United Kingdom

Objectives The aim of this study was to evaluate the prognostic value of high-sensitivity troponin T (hs-TnT) in addition to clinical risk factors and the CHA_2DS_2VASc (congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female) risk score in patients with atrial fibrillation (AF).

Background The level of troponin is a powerful predictor of cardiovascular events and mortality.

Methods A total of 14,897 patients with AF were randomized to treatment with apixaban or warfarin in the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial. The associations between baseline hs-TnT levels and outcomes were evaluated using adjusted Cox regression models.

Results Levels of hs-TnT were measurable in 93.5% of patients; 75% had levels >7.5 ng/l, 50% had levels >11.0 ng/l, and 25% had levels >16.7 ng/l. During a median 1.9-year period, the annual rates of stroke or systemic embolism ranged from 0.87% in the lowest hs-TnT quartile to 2.13% in the highest hs-TnT quartile (adjusted hazard ratio [HR]: 1.94; 95% confidence interval [CI]: 1.35 to 2.78; $p = 0.0010$). The annual rates in the corresponding groups ranged from 0.46% to 4.24% (adjusted HR: 4.31; 95% CI: 2.91 to 6.37; $p < 0.0001$) for cardiac death and from 1.26% to 4.21% (adjusted HR: 1.91; 95% CI: 1.43 to 2.56; $p = 0.0001$) for major bleeding. Adding hs-TnT levels to the CHA_2DS_2VASc score improved the C statistic from 0.620 to 0.635 for stroke or systemic embolism ($p = 0.0226$), from 0.592 to 0.711 for cardiac death ($p < 0.0001$), and from 0.591 to 0.629 for major bleeding ($p < 0.0001$). Apixaban reduced rates of stroke, mortality, and bleeding regardless of the hs-TnT level.

Conclusions Levels of hs-TnT are often elevated in patients with AF. The hs-TnT level is independently associated with an increased risk of stroke, cardiac death, and major bleeding and improves risk stratification beyond the CHA_2DS_2VASc risk score. The benefits of apixaban as compared with warfarin are consistent regardless of the hs-TnT level. (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation [ARISTOTLE]; NCT00412984) (J Am Coll Cardiol 2014;63:52–61) © 2014 by the American College of Cardiology Foundation

From the *Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; †Section of Cardiology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden; ‡Section of Clinical Chemistry, Department of Medical Sciences, Uppsala University, Uppsala, Sweden; §Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; ‖Department of Cardiology, Oslo University Hospital Ulleval and Faculty of Medicine, Institute for Clinical Medicine, University of Oslo, Oslo, Norway; ¶Mayo Clinic College of Medicine, Rochester, Minnesota; #Bristol-Myers Squibb, Princeton, New Jersey; **Division of Emergency Care, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland; ††University of Adelaide, Adelaide, South Australia, Australia; ‡‡Medical Department, Hospital Unit West, Herning/Holstbro, Denmark; §§Boston University Medical Center, Boston, Massachusetts; and the ‖‖BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, United Kingdom. The trial was funded by Bristol-Myers Squibb and Pfizer and coordinated by the Duke Clinical Research Institute and Uppsala Clinical Research Center. Both academic research institutes and the sponsors had full access to the database. Uppsala Clinical Research Center received funding from Bristol-Myers Squibb for the independent statistical analysis performed by Dr. Andersson. Dr. Hijazi has received lecture fees and an institutional research grant from Boehringer Ingelheim. Dr. Wallentin has received research grants from AstraZeneca, Merck & Co., Boehringer

Atrial fibrillation (AF) is associated with an increased risk of stroke and cardiovascular mortality (1). Treatment with oral anticoagulation is recommended for prevention of stroke if the protective effects outweigh the risk of severe bleeding (2). The availability of new oral anticoagulants that provide a further reduction in the risk of stroke and mortality and a lower risk of intracranial bleeding might widen the indications for oral anticoagulation because of a better balance between benefits and risks as compared with warfarin (3,4). Over the past decade, the risk of stroke in patients with AF has been estimated by the $CHADS_2$ (congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack) risk score, integrating the risk factors of congestive heart failure, hypertension, ≥75 years of age, diabetes mellitus, and previous stroke (×2) (5). The score classification has recently been expanded by adding the risk factors of 65 to 74 years of age, female sex, and vascular disease, now featured in the CHA_2DS_2VASc (congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female) score (6). In addition, the use of the complementary HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score for evaluation of bleeding risk has been recommended (2). Currently, the occurrence of at least 1 $CHADS_2$ risk factor or a score of 2 according to CHA_2DS_2-VASc is considered an indication for oral anticoagulation for prevention of stroke in patients with AF.

It was recently proposed that the addition of biomarker information (i.e., troponin and N-terminal pro-brain natriuretic peptide levels) might improve the discriminatory information concerning ischemic events, mortality, and bleeding in patients with AF treated with anticoagulation (7). The next generation of high-sensitivity troponin assays is becoming available worldwide, allowing detection and measurement of troponin levels with high levels of precision in almost all subjects (8,9). Information on the high-sensitivity troponin T (hs-TnT) level has improved the prognostic information not only in patients with chest pain and acute coronary syndromes but also in patients with conditions such as congestive heart failure and stable atherosclerotic disease and even in apparently healthy elderly subjects (10–16). In the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial, we obtained plasma samples for central biomarker analyses from 14,897 of 18,201 patients (4,17). In this pre-specified substudy, we assessed the associations between hs-TnT levels at baseline and clinical outcomes after adjusting for established cardiovascular risk factors. We also compared the prognostic information with that of the CHA_2DS_2VASc score and evaluated the outcomes with apixaban as compared with warfarin in relation to levels of hs-TnT.

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
HR = hazard ratio
hs-TnT = high-sensitivity troponin T
IDI = integrated discrimination improvement measure
NRI = net reclassification improvement

Methods

The ARISTOTLE trial. The details of the ARISTOTLE trial have been published previously (17). Briefly, ARISTOTLE was a double-blind, double-dummy, randomized clinical trial that enrolled 18,201 patients with AF and at least one $CHADS_2$ risk factor for stroke or systemic embolism. Patients were randomized to treatment with 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

Ingelheim, Bristol-Myers Squibb/Pfizer, and GlaxoSmithKline; served as a consultant for Merck & Co., Regado Biosciences, Evolva, Portola, CSL Behring, Athera Biotechnologies, Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, and Bristol-Myers Squibb/Pfizer; received lecture fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and Merck & Co.; received honoraria from Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and Merck & Co.; and received travel support from AstraZeneca and Bristol-Myers Squibb/Pfizer. Dr. Siegbahn has received institutional research grants from AstraZeneca, Boehringer Ingelheim, and Bristol-Myers Squibb; and research grants from AstraZeneca and Boehringer Ingelheim. Dr. Alexander has received grants from Bristol-Myers Squibb/Pfizer, CSL Behring, Merck/Schering-Plough, and Regado Biosciences; travel support from Bristol-Myers Squibb; and consulting fees from Bristol-Myers Squibb/Pfizer, CSL Behring, Merck/Schering-Plough, AstraZeneca, Boehringer Ingelheim, Ortho-McNeil-Janssen Pharmaceuticals, PolyMedix, Regado Biosciences, Bayer, and Daiichi Sankyo. Dr. Atar has received honoraria from Siemens Bioscience, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Nycomed-Takeda. Dr. Gersh has served as a consultant for Ortho-McNeil-Janssen Pharmaceuticals, GE Healthcare, St. Jude Medical, Abbott Laboratories, Medispec, Merck & Co., and Boston Scientific; and has served on the data and safety monitoring board for Pharmaceutical Product Development, Cardiovascular Research Foundation, InspireMD, Boston Scientific, Baxter Healthcare, and St. Jude Medical. Dr. Hanna is an employee of Bristol-Myers Squibb and receives stock as a part of compensation. Dr. Harjola has received consulting and lecture fees from Abbott Laboratories, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Novartis, and Orion Pharma; and is an advisory board member for Roche Diagnostics in Finland. Dr. Horowitz has received consulting fees and travel support and is an executive committee member for Bristol-Myers Squibb; and has received lecture fees from Bristol-Myers Squibb and Pfizer. Dr. Husted is an advisory board member for Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb, Pfizer, and Bayer; and has received research support from GlaxoSmithKline, Bristol-Myers Squibb, Pfizer, Bayer, Boehringer Ingelheim, and Sanofi-Aventis. Dr. Hylek has received consulting fees and travel support and is an adjudication committee member for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck & Co., Ortho-McNeil, Johnson & Johnson, and Pfizer; and has received lecture fees from Boehringer Ingelheim. Dr. Lopes has received grants from Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, and Daiichi Sankyo; and consulting fees from Bristol-Myers Squibb/Pfizer and Boehringer Ingelheim. Dr. McMurray has received a research grant from Bristol-Myers Squibb/Pfizer. Dr. Granger has received grants from Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic Foundation, Merck & Co., Pfizer, Sanofi-Aventis, Takeda, and The Medicines Company; and has received consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Ross Medical Corp., GlaxoSmithKline, Hoffmann-La Roche, Novartis Pharmaceutical Company, Lilly, Pfizer, Sanofi-Aventis, Takeda, The Medicines Company, and AstraZeneca. All other authors have reported that they have no relationships relevant to the content of this paper to disclose.

Manuscript received May 15, 2013; revised manuscript received July 6, 2013, accepted July 23, 2013.

Haemostasis criteria. The median length of follow-up was 1.9 years in the biomarker substudy.

Endpoints and clinical risk classification. The endpoints 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), and major bleeding based on the International Society on Thrombosis and Haemostasis criteria; composites included stroke or systemic embolism, total death or cardiac death, and myocardial infarction. A blinded clinical events committee adjudicated all endpoints using pre-specified criteria (17). $CHADS_2$ and CHA_2DS_2VASc scores were calculated for each patient based on the sum of the corresponding risk factors present at randomization. Patients were classified by $CHADS_2$ (low risk: 0 to 1; medium risk: 2; high risk: $\geq$3) and CHA_2DS_2VASc scores (very low risk: 0 to 1; low risk: 2; medium risk: 3; elevated risk: 4; high risk: $\geq$5). Outcomes in relation to HAS-BLED scores were also evaluated as a sensitivity analysis.

Biochemical methods. All patients were required to provide plasma samples at randomization, and the samples were frozen in aliquots and stored at −70°C until analyzed centrally. The hs-TnT levels were determined with sandwich immunoassays using the Cobas Analytics e601 Immunoanalyzer (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. According to the manufacturer, the limit of the blank with this assay is 3 ng/l and the limit of detection is 5 ng/l. The coefficient of variation is <10% at 14 ng/l, the 99th percentile upper reference limit for healthy subjects.

Statistical analyses. These analyses included the 14,897 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 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 hs-TnT as the response variable and categorized baseline characteristics as the 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 cutoff 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 incidences of the different endpoints were summarized in relation to randomized treatment, quartiles of the hs-TnT levels, and CHA_2DS_2VASc and HAS-BLED scores as outlined in the preceding text.

The outcomes in relation to treatment and hs-TnT subgroups were analyzed using a Cox proportional hazards model, including treatment group, hs-TnT quartile group, and treatment by hs-TnT interaction as covariates. The estimated hazard ratios (HRs) were used to assess the treatment effect in each of the subgroups, and the significance of the biomarker interacting with the effect of treatment was judged by the significance of the interaction statistic. The outcomes in relation to hs-TnT quartiles were evaluated both in a multivariable Cox proportional hazards model and a model including randomized treatment and CHA_2DS_2VASc score. 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 graft/percutaneous coronary intervention, and treatment at randomization with aspirin, an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, or amiodarone for the major bleeding endpoint; a history of anemia and a history of spontaneous or clinical relevant bleeding were also included), randomized treatment, region, use of warfarin within 7 days before randomization, use of a statin medication within 30 days before determination of the randomization score, and biomarkers (cystatin C and N-terminal pro-brain natriuretic peptide levels). The HRs and 95% confidence intervals (CIs), using the group with the lowest hs-TnT levels as reference, were reported.

The increased discriminative value of hs-TnT was investigated by estimating the difference in C statistics between models with and without biomarkers as well as the integrated discrimination improvement measure (IDI) as described by Pencina et al. (18,19). In these analyses, an occurrence/nonoccurrence of an event, respectively, 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 (20). In addition, continuous (category-free) net reclassification improvement (NRI) was analyzed as a measure of the probability of better reclassification minus the probability of worse reclassification with the new model. The NRI among events and among nonevents as well as the total NRI were analyzed.

Likelihood ratio tests were performed to evaluate whether the global model fit improved after the addition of hs-TnT.

Kaplan-Meier estimates of the cumulative hazard rate were calculated and plotted. All 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 Clinical Trials Section at Uppsala Clinical Research Center, Uppsala, Sweden, conducted the statistical analyses using SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina).

Results

Baseline characteristics and distribution of hs-TnT levels. The distribution of hs-TnT levels showed a mean of 14.5 ng/l and a median of 11.0 ng/l (25th percentile: 7.5 ng/l; 75th percentile: 16.7 ng/l) in the total population without any differences between the randomized treatment groups. Thus, 93.5% of the patients had measurable hs-TnT levels; 50% had levels >11.0 ng/l, and 25% had levels >16.7 ng/l.

Baseline characteristics and medications according to quartiles of hs-TnT are shown in Table 1. Age, male sex, higher body mass index, diabetes mellitus, congestive heart failure, permanent or persistent AF, prior vascular disease (stroke, peripheral arterial disease, coronary artery disease), and renal impairment had the strongest independent relationships to the hs-TnT level on multivariable analysis ($p < 0.001$ for all). Except for hypertension, all risk factors that constitute the $CHADS_2$ and CHA_2DS_2VASc scores were more common in patients with higher hs-TnT levels. Accordingly, among patients with hs-TnT levels >16.7 ng/l, 83.6% had a CHA_2DS_2VASc score >2, in contrast to only 54.7% in patients with hs-TnT levels ≤7.5 ng/l.

hs-TnT levels in relation to outcome events. In this substudy cohort, there were 397 stroke or systemic embolism events (1.40%/year), 1,075 total deaths (3.69%/year), 547 cardiac deaths (1.88%/year), 150 myocardial infarctions (0.52%/year), and 674 events of major bleeding (2.61%/year).

Table 1 Summary of Demographic and Baseline Characteristics According to High-Sensitivity Troponin T Level at Baseline

	High-Sensitivity Troponin T Level (ng/l)				
	≤7.5	>7.5–11.0	>11.0–16.7	>16.7	p Value
n	3,771	3,747	3,682	3,697	
Age (yrs)	64.0 (58.0, 70.0)	70.0 (63.0, 75.0)	72.0 (66.0, 77.0)	74.0 (67.0, 79.0)	<0.0001
Male	2,027 (53.8)	2,352 (62.8)	2,455 (66.7)	2,758 (74.6)	<0.0001
Weight (kg)	82.9 (70.0, 95.8)	82.0 (70.0, 95.0)	82.0 (70.0, 96.0)	82.0 (70.0, 96.0)	0.6862
Permanent or persistent atrial fibrillation	2,962 (78.5)	3,161 (84.4)	3,224 (87.6)	3,294 (89.1)	<0.0001
Calculated CrCl (ml/min)	87.0 (68.8, 109.8)	76.7 (60.9, 97.7)	70.3 (54.2, 89.4)	62.2 (46.8, 80.9)	<0.0001
$CHADS_2$ risk factors					
CHF or LVEF ≤40%	1,066 (28.3)	1,160 (31.0)	1,377 (37.4)	1,742 (47.1)	<0.0001
Hypertension	3,315 (87.9)	3,276 (87.4)	3,225 (87.6)	3,222 (87.2)	0.7960
≥75 yrs of age	472 (12.5)	989 (26.4)	1,399 (38.0)	1,709 (46.2)	<0.0001
Diabetes mellitus	693 (18.4)	852 (22.7)	945 (25.7)	1,189 (32.2)	<0.0001
Prior stroke or TIA	618 (16.4)	673 (18.0)	728 (19.8)	776 (21.0)	<0.0001
CHA_2DS_2VASc risk factors					
65–74 yrs of age	1,371 (36.4)	1,642 (43.8)	1,507 (40.9)	1,319 (35.7)	<0.0001
Female	1,744 (46.2)	1,395 (37.2)	1,227 (33.3)	939 (25.4)	<0.0001
Myocardial infarction	249 (6.6)	415 (11.1)	545 (14.8)	705 (19.1)	<0.0001
Previous PCI/CABG	264 (7.0)	469 (12.5)	542 (14.7)	746 (20.2)	<0.0001
Peripheral arterial disease	88 (2.3)	146 (3.9)	203 (5.5)	287 (7.8)	<0.0001
$CHADS_2$ score					
≤1	1,861 (49.4)	1,431 (38.2)	1,042 (28.3)	723 (19.6)	<0.0001
2	1,194 (31.7)	1,358 (36.2)	1,410 (38.3)	1,412 (38.2)	
≥3	716 (19.0)	958 (25.6)	1,230 (33.4)	1,562 (42.3)	
CHA_2DS_2VASc score					
≤1	627 (16.6)	329 (8.8)	200 (5.4)	143 (3.9)	<0.0001
2	1,082 (28.7)	885 (23.6)	669 (18.2)	463 (12.5)	
3	947 (25.1)	994 (26.5)	962 (26.1)	968 (26.2)	
4	644 (17.1)	821 (21.9)	912 (24.8)	926 (25.0)	
≥5	471 (12.5)	718 (19.2)	939 (25.5)	1,197 (32.4)	
Medications at randomization					
Aspirin	1,073 (28.5)	1,103 (29.4)	1,166 (31.7)	1,262 (34.1)	<0.0001
Warfarin	1,999 (53.2)	2,085 (55.7)	1,961 (53.4)	1,959 (53.0)	0.0615
ACE inhibitor or ARB	2,519 (66.8)	2,597 (69.3)	2,622 (71.2)	2,802 (75.8)	<0.0001
Calcium-channel blocker	1,206 (32.0)	1,180 (31.5)	1,144 (31.1)	1,023 (27.7)	0.0002
Beta blocker	2,431 (64.5)	2,388 (63.7)	2,310 (62.7)	2,288 (61.9)	0.1056
Digoxin	904 (24.0)	1,081 (28.8)	1,316 (35.7)	1,528 (41.3)	<0.0001

Values are median (25th percentile, 75th percentile) or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; CHADS2 = congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack; CHA_2DS_2VASc = congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female; CHF = congestive heart failure; CrCl = creatinine clearance; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

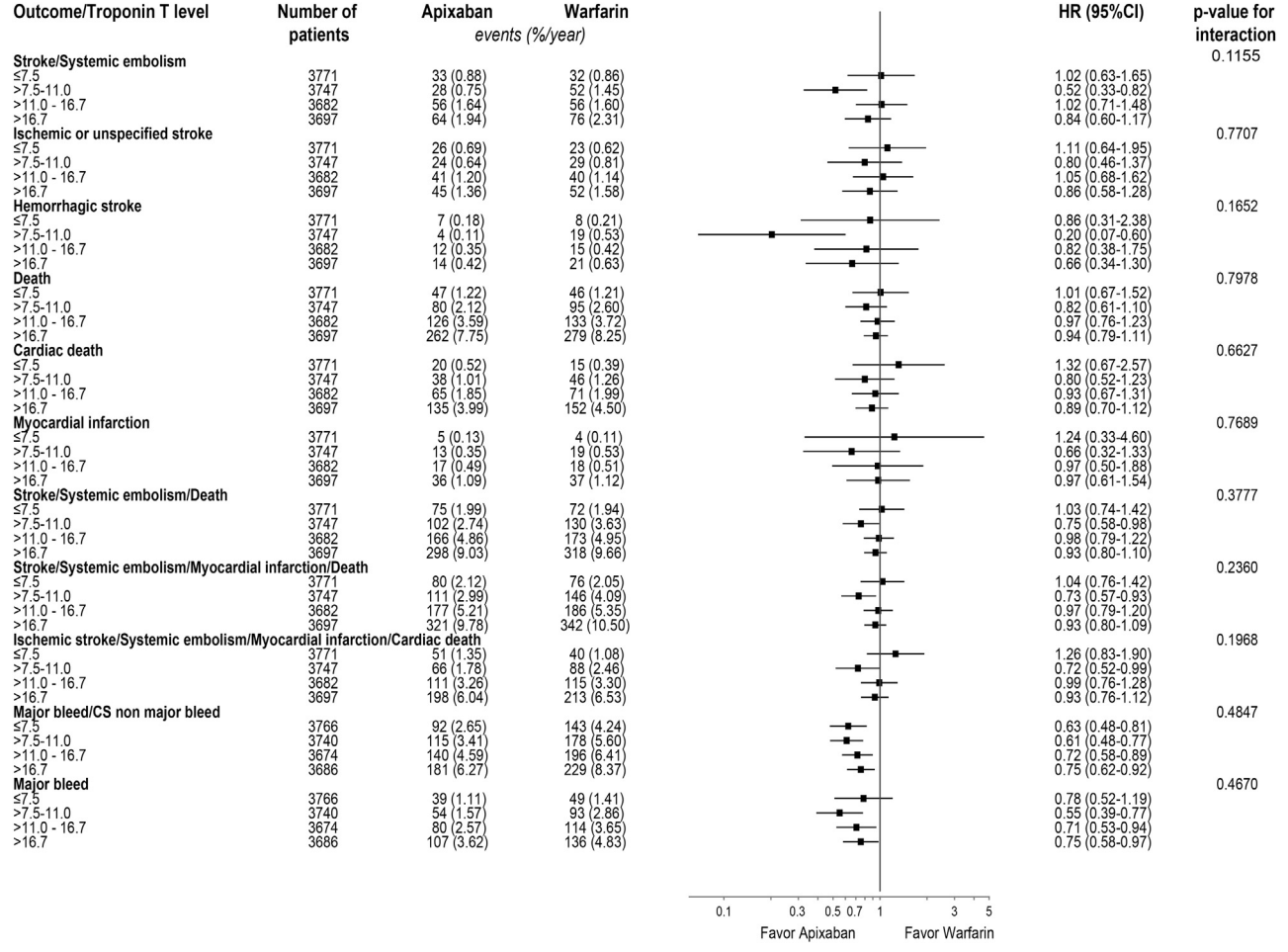

Figure 1 **Efficacy of Apixaban Relative to Warfarin in Relation to High-Sensitivity Troponin T Level at Baseline**

Cox proportional hazards model with biomarker level, treatment, and interaction between treatment and biomarker level as covariates. CI = confidence interval; CS = clinically significant; HR = hazard ratio.

When comparing the outcomes in relation to the randomized treatments, there was no significant interaction with the hs-TnT levels at baseline (Fig. 1). Thus, there were consistent reductions in rates of stroke, hemorrhagic stroke, total mortality, composites of these events, and major bleeding across the range of hs-TnT levels (all interaction p values >0.10). When evaluating the association between hs-TnT levels and outcomes, the randomized treatment groups were therefore combined and adjusted for in the multivariable analyses.

Higher hs-TnT levels were strongly and significantly associated with a higher rate of all outcome events even after adjustment for baseline characteristics and indicators of myocardial and renal dysfunction in the multivariable model (Fig. 2). In regard to stroke, the risk was significantly higher in patients with hs-TnT levels >11.0 ng/l and almost doubled in the group with hs-TnT levels >16.7 ng/l as compared with the group with hs-TnT levels <7.5 ng/l with an adjusted HR of 1.94 (95% CI: 1.35 to 2.78; p = 0.0010 for effect of hs-TnT). This increased risk of stroke was driven mainly by higher rates of ischemic stroke. Cardiac mortality increased gradually with higher hs-TnT levels, reaching an adjusted HR of 4.31 (95% CI: 2.91 to 6.37; p < 0.0001) in the group with hs-TnT levels >16.7 ng/l versus the lowest quartile hs-TnT group. Despite the overall low event rates, there was a similar association between hs-TnT levels and subsequent myocardial infarction, with a significantly raised risk with higher hs-TnT levels and an adjusted HR of 5.52 (95% CI: 2.56 to 11.92) in the group with hs-TnT levels >16.7 ng/l versus the lowest quartile hs-TnT group. The rates of the composite of the individual events showed correspondingly strongly significant associations with increasing hs-TnT levels. Also, the rate of major bleeding displayed a gradual relationship to increased hs-TnT levels and an adjusted HR of 1.91 (95% CI: 1.43 to 2.56) in the group with the highest versus lowest quartile hs-TnT group. Similar results were obtained when adjusting for the HAS-BLED

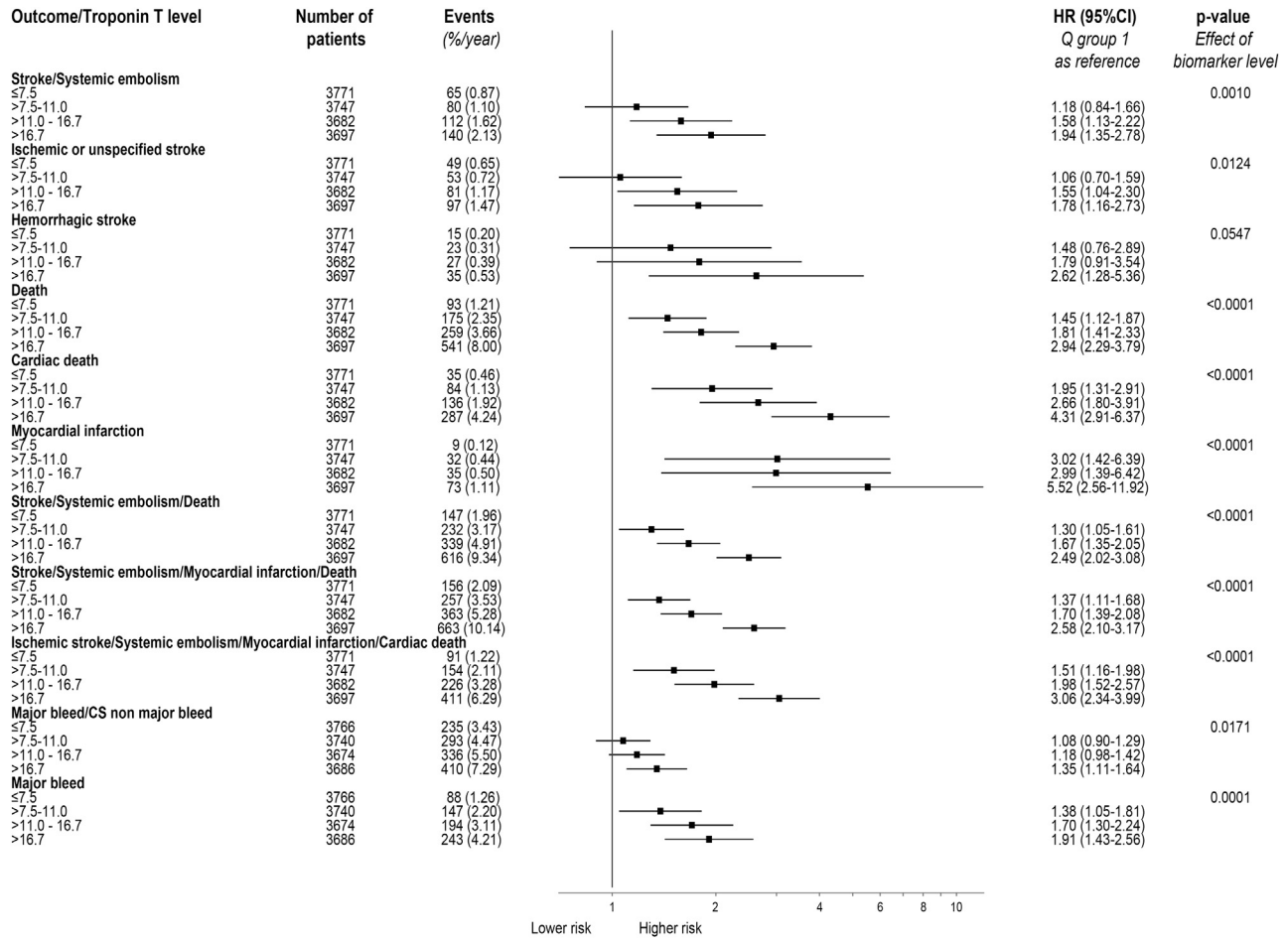

Figure 2 **The Relationship Between High-Sensitivity Troponin T Level at Baseline and Outcomes**

Cox proportional hazards model adjusted for established risk factors (age, sex, body mass index, smoking status, systolic blood pressure, heart rate, type of atrial fibrillation, diabetes, heart failure, previous stroke/systemic embolism/transient ischemic attack, hypertension, previous myocardial infarction, previous peripheral arterial disease/coronary artery bypass graft/percutaneous coronary intervention, and treatment at randomization with aspirin, an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, or amiodarone for the major bleeding endpoint; a history of anemia and a 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 determination of the randomization score, and biomarkers (cystatin C and N-terminal pro-brain natriuretic peptide). Q = quartile; other abbreviations as in Figure 1.

score (results not shown). As illustrated in the Kaplan-Meier plots (Figs. 3A to 3C), the associations between hs-TnT levels at baseline and the risk of subsequent events remained stable over time.

hs-TnT level and CHA_2DS_2VASc score. Annual rates of stroke or systemic embolism according to hs-TnT level and CHA_2DS_2VASc score are illustrated in Figure 4. The rate increased with both increasing CHA_2DS_2VASc score and higher hs-TnT level. The highest annual rate of stroke and systemic embolism, ≥2%/year, was found in the group with a CHA_2DS_2VASc score >4 or hs-TnT level >11.0 ng/l compared with an average annual rate of <0.4% in the group with a CHA_2DS_2VASc score ≤2 and hs-TnT level ≤11.0 ng/l (Fig. 4A). Thus, the hs-TnT level and CHA_2DS_2-VASc score provided statistically significant independent prognostic information; the C statistic was 0.620 (95% CI: 0.592 to 0.647) for the CHA_2DS_2VASc score alone and not significantly different from 0.591 (95% CI: 0.564 to 0.619) ($p = 0.1080$) for the hs-TnT level alone and increased significantly to 0.635 (95% CI: 0.609 to 0.661), corresponding to a relative IDI improvement of 23.0% ($p = 0.0010$) by adding the hs-TnT level to the CHA_2DS_2VASc score. There was a significant improvement in reclassification by addition of the hs-TnT level based on continuous NRI analyses (27.4% [95% CI: 17.7% to 37.1%; $p < 0.0001$) for stroke or systemic embolism, mainly due to events contributing (23.9%).

For cardiac mortality, increasing hs-TnT level had a larger impact on outcomes than the CHA_2DS_2VASc score (Fig. 4B), with a C statistic of 0.592 (95% CI: 0.567 to 0.616) for the CHA_2DS_2VASc score alone and significantly higher at 0.699 (95% CI: 0.678 to 0.719)

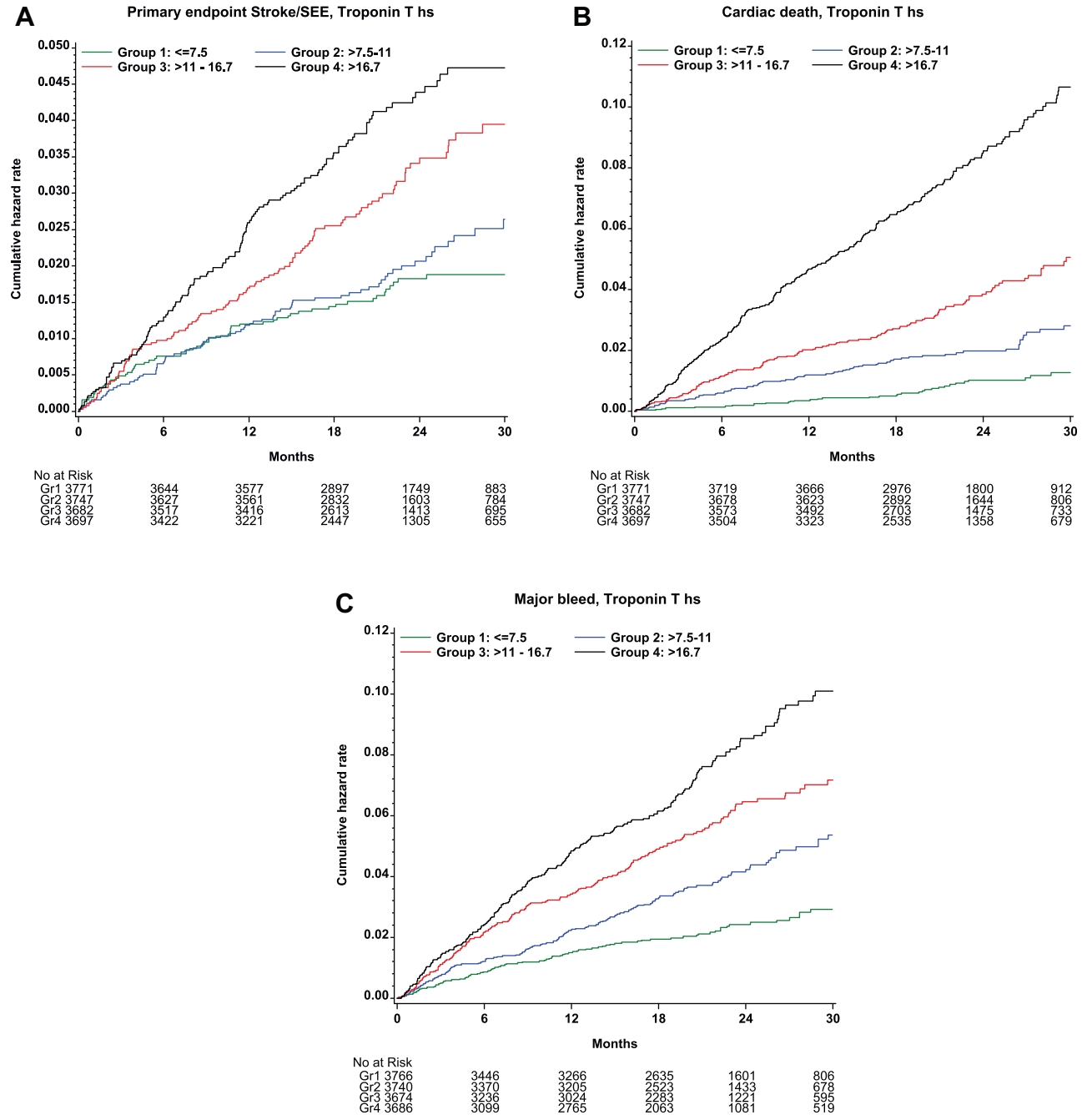

Figure 3 **Cumulative Hazard Rates According to High-Sensitivity Troponin T Quartiles**

Cumulative hazard rates for **(A)** the primary outcome (stroke or systemic embolism [SEE]), **(B)** cardiac death, and **(C)** major bleeding by high-sensitivity (hs) troponin T level at baseline.

($p < 0.0001$) for the hs-TnT level alone. The C statistic increased significantly to 0.711 (95% CI: 0.690 to 0.733), corresponding to a relative IDI improvement of 314.9% ($p < 0.0001$) and NRI of 56.6% (95% CI: 48.4% to 64.8%; $p < 0.0001$) by adding the hs-TnT level to the CHA_2DS_2VASc score. Accordingly, for the composite of ischemic events and mortality, an increasing hs-TnT level had a stronger association with outcomes than the CHA_2DS_2VASc score, with a C statistic of 0.597 for the CHA_2DS_2VASc score alone, which was significantly higher for the hs-TnT level alone at 0.660 (95% CI: 0.642 to 0.678) ($p < 0.0001$) and increasing to 0.675 (95% CI: 0.657 to 0.693), corresponding to a relative IDI improvement of 207.9% ($p < 0.0001$) by adding the

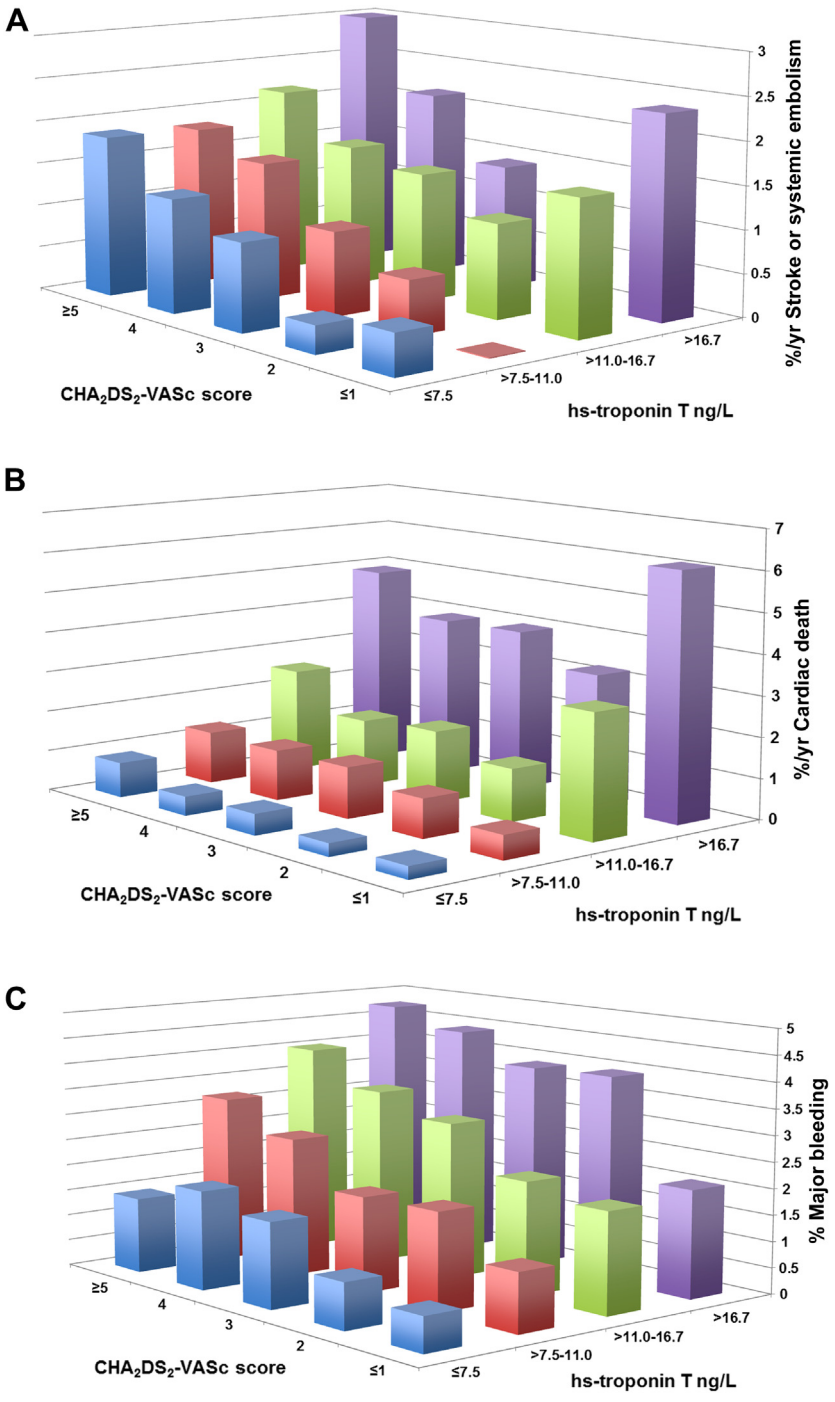

Figure 4 **High-Sensitivity Troponin T Quartiles in Relation to the CHA_2DS_2-VASc Score**

Annual event rates for **(A)** stroke or systemic embolism, **(B)** cardiac death, and **(C)** major bleeding in relation to levels of high-sensitivity (hs) troponin T and the CHA_2DS_2-VASc risk score stratified as 0 to 1/2/3/4/≥5. The numbers of patients in the rising hs troponin T quartiles with a CHA_2DS_2-VASc score of 0 to 1 were 625, 325, 205, and 143; with a score of 2 were 1,137, 805, 685, and 472; with a score of 3 were 1,039, 888, 947, and 994; with a score of 4 were 713, 750, 939, and 898; and with a score ≥5 were 560, 662, 909, and 1,195, respectively. CHA_2DS_2-VASc = congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female.

hs-TnT level to the CHA_2DS_2VASc score. Also, regarding major bleeding, there was a consistent increase with both increasing hs-TnT and CHA_2DS_2VASc score groups (Fig. 4C). The C statistic was 0.591 for the CHA_2DS_2VASc score alone, which was significantly higher than 0.617 (95% CI: 0.596 to 0.637) ($p = 0.0319$)

for the hs-TnT level alone, and increased to 0.629 (95% CI: 0.609 to 0.650), corresponding to a relative IDI improvement of 84% ($p < 0.0001$) by adding the hs-TnT level to the CHA_2DS_2VASc score.

For all outcomes, likelihood ratio tests showed that the global model fit improved after the addition of hs-TnT level (all $p < 0.001$).

Discussion

The present study showed that hs-TnT levels can be detected in almost all patients (93.5%) with AF and at least 1 clinical risk factor for stroke. The level of hs-TnT was related to many clinical risk factors, such as age, male sex, higher body mass index, diabetes mellitus, prior vascular disease, permanent or persistent AF, and indicators of myocardial and renal dysfunction. Even after adjustment for these factors, the level of hs-TnT carried strong prognostic information with a gradual increase in the risk of stroke, cardiac and total death, myocardial infarction, and major bleeding with rising hs-TnT levels. An increased risk of stroke was present at hs-TnT levels above the median (11.0 ng/l), whereas raised risks of myocardial infarction, cardiac and total mortality, and major bleeding were seen at even lower hs-TnT levels (>7.5 ng/l). In regard to cardiac mortality, myocardial infarction, and major bleeding, the hs-TnT level alone provided better prognostic information than did the CHA_2DS_2VASc risk score. The combination of the hs-TnT level with the CHA_2DS_2VASc risk score, however, allowed improved identification of patients at lower and higher risk of stroke compared with either indicator alone. There was no interaction between risk stratification by hs-TnT level and the superior efficacy and safety of apixaban as compared with warfarin. Therefore, there was a larger absolute reduction in stroke, mortality, and major bleeding in patients at higher risk (e.g., as identified by higher hs-TnT levels).

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 in the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial (7). The considerably larger number of patients and the more sensitive troponin assay in the present study (n = 14,897) as compared with the RE-LY biomarker study (n = 6,189) provided a greater discriminatory power in regard to the relationship between hs-TnT levels and individual outcome events and also in the comparison and combination with the CHA_2DS_2VASc score. In regard to stroke, the hs-TnT level and CHA_2DS_2VASc score provided complementary information, with the lowest risk in those having both a low hs-TnT level (<11.0 ng/l) and a low CHA_2DS_2VASc score (≤2). It is noteworthy that the determination of hs-TnT level among patients with a low CHA_2DS_2VASc score (≤2) can identify patients at risks for stroke and major bleeding similar to those among patients with CHA_2DS_2VASc scores >3. Likewise, it is remarkable that, concerning stroke, the CHA_2DS_2VASc score provides further risk stratification within all hs-TnT subgroups. This information will therefore immediately be clinically useful because it allows for the identification of patients with low CHA_2DS_2VASc scores who nevertheless are at high risk for stroke. This should improve therapeutic decision making related to oral anticoagulation.

Concerning cardiac mortality, myocardial infarction, and even major bleeding, the hs-TnT level provided more prognostic information than did the CHA_2DS_2VASc score. This emphasizes that the clinical characteristics included in the CHA_2DS_2VASc risk score have been identified to provide information on the risk of stroke but only contribute limited information on the risk of other events of major clinical importance for patients with AF. By the inclusion of hs-TnT level in the risk-stratification process, additional information on the risk of cardiac and total mortality and myocardial infarction and better prognostication of the risk of bleeding will be provided. This information should therefore also be immediately useful in decision making concerning oral anticoagulants and even other medical treatments for individual patients with AF.

Consistent results from 2 large-scale prospective trials, together including 21,081 patients, provide definitive evidence for the incremental prognostic value of hs-TnT levels for stroke, cardiac and total death, other ischemic events, and major bleeding in patients with AF (3,4,7). The independent prognostic value of the hs-TnT levels is also validated by similar findings in healthy elderly subjects, patients with acute and chronic atherosclerotic diseases, and patients with congestive heart failure (10,11,13–16). The underlying mechanisms for this independent relationship are probably multifactorial because the level of hs-TnT is related to aging and tissue vulnerability, myocardial necrosis and apoptosis, myocardial stress (e.g., due to increased or variable heart rates), myocardial dysfunction with variations in atrial and ventricular volume and pressure load, and episodes of myocardial ischemia (e.g., due to microembolism) (2,21–24). There might also be an association with underlying inflammatory and fibrotic processes, including endothelial dysfunction and a hypercoagulable state, that might contribute to both AF and the risk of thromboembolism (25,26). However, even without a complete understanding of the underlying mechanisms, the firm evidence of the incremental prognostic value of hs-TnT for risk stratification and the availability of this test in almost every hospital worldwide should make it a very attractive tool to include as decision support for selection of treatment in patients with AF.

Study limitations. All patients were treated with oral anticoagulation, which impairs the opportunity to provide clear recommendations on which patients might benefit, or not, from this type of treatment. Also, our results were based on a clinical trial population, which will be somewhat different and generally at lower risk than an unselected clinical patient population.

Conclusions

In patients with AF treated with oral anticoagulation, the level of hs-TnT, even within the normal range, is gradually and independently related to the risk of stroke, myocardial infarction, cardiac and total death, and major bleeding. The combination of the hs-TnT level and the CHA_2DS_2VASc risk score allows improved and safer identification of patients both at very low risk and at higher risk for stroke, whereas the hs-TnT level alone carries most of the information on the risk of other ischemic events, cardiac mortality, and bleeding. The benefits of apixaban as compared with warfarin are consistent regardless of the hs-TnT level. The combination of the hs-TnT level and the CHA_2DS_2VASc risk score might provide improved decision support concerning anticoagulant and other treatments in patients with AF.

Acknowledgment

The authors thank Ulla Nässander Schikan, PhD (Uppsala Clinical Research Center, Uppsala, Sweden), for editorial assistance.

Reprint requests and correspondence: Dr. Ziad Hijazi, Uppsala Clinical Research Center, Dag Hammarskjölds väg 14B 1 tr, SE-752 37 Uppsala, Sweden. E-mail: ziad.hijazi@ucr.uu.se.

REFERENCES

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946–52.
2. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369–429.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
4. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.
5. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
6. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263–72.
7. Hijazi Z, Oldgren J, Andersson U, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) substudy. Circulation 2012;125:1605–16.
8. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56:254–61.
9. Venge P, Johnston N, Lindahl B, James S. Normal plasma levels of cardiac troponin I measured by the high-sensitivity cardiac troponin I access prototype assay and the impact on the diagnosis of myocardial ischemia. J Am Coll Cardiol 2009;54:1165–72.
10. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503–12.
11. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304:2494–502.
12. Januzzi JL Jr., Bamberg F, Lee H, et al. High-sensitivity troponin T concentrations in acute chest pain patients evaluated with cardiac computed tomography. Circulation 2010;121:1227–34.
13. Latini R, Masson S, Anand IS, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 2007;116:1242–9.
14. Lindahl B, Venge P, James S. The new high-sensitivity cardiac troponin T assay improves risk assessment in acute coronary syndromes. Am Heart J 2010;160:224–9.
15. Omland T, de Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 2009;361:2538–47.
16. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858–67.
17. Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for reduction in stroke and other ThromboembolLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J 2010;159:331–9.
18. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.
19. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72; discussion 207–12.
20. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Comments on 'integrated discrimination and net reclassification improvements—practical advice'. Stat Med 2008;27:207–12.
21. Dobrev D, Nattel S. Calcium handling abnormalities in atrial fibrillation as a target for innovative therapeutics. J Cardiovasc Pharmacol 2008;52:293–9.
22. Eggers KM, Lind L, Ahlstrom H, et al. Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. Eur Heart J 2008;29:2252–8.
23. Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. Ann Intern Med 2005;142:786–91.
24. Pirat B, Atar I, Ertan C, et al. Comparison of C-reactive protein levels in patients who do and do not develop atrial fibrillation during electrophysiologic study. Am J Cardiol 2007;100:1552–5.
25. Asakura H, Hifumi S, Jokaji H, et al. Prothrombin fragment F1 + 2 and thrombin-antithrombin III complex are useful markers of the hypercoagulable state in atrial fibrillation. Blood Coagul Fibrinolysis 1992;3:469–73.
26. Conway DS, Pearce LA, Chin BS, Hart RG, Lip GY. Plasma von Willebrand factor and soluble p-selectin as indices of endothelial damage and platelet activation in 1321 patients with nonvalvular atrial fibrillation: relationship to stroke risk factors. Circulation 2002;106:1962–7.

Key Words: atrial fibrillation ■ cardiac troponin ■ high-sensitivity troponin T ■ risk stratification ■ stroke risk.