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ORIGINAL RESEARCH

Repeated Measurement of the Novel Atrial Biomarker BMP10 (Bone Morphogenetic Protein 10) Refines Risk Stratification in Anticoagulated Patients With Atrial Fibrillation: Insights From the ARISTOTLE Trial

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BACKGROUND: BMP10 (bone morphogenic protein 10) has emerged as a novel biomarker associated with the risk of ischemic stroke and other outcomes in patients with atrial fibrillation (AF). The study aimed to determine if repeated BMP10 measurements improve prognostication of cardiovascular events in patients with AF.

METHODS AND RESULTS: BMP10 was measured using a prototype Elecsys immunoassay in plasma samples collected at randomization and after 2 months in patients with AF randomized to apixaban or warfarin in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (n=2878). Adjusted Cox-regression models were used to evaluate the association between 2-month BMP10 levels and outcomes. BMP10 levels increased by 7.8% (P<0.001) over 2 months. The baseline variables most strongly associated with BMP10 levels at 2 months were baseline BMP10 levels, body mass index, sex, age, creatinine, diabetes, warfarin treatment, and AF-rhythm. During median 1.8 years follow-up, 34 ischemic strokes/systemic embolism, 155 deaths, and 99 heart failure hospitalizations occurred. Comparing the third with the first sample quartile, higher BMP10 levels at 2 months were associated with higher risk of ischemic stroke (hazard ratio [HR], 1.33 [95% CI, 0.67–2.63], P=0.037), heart failure (HR, 1.91 [95% CI, 1.17–3.12], P=0.012) and all-cause death (HR, 1.61 [95% CI, 1.17–2.21], P<0.001). Adding BMP10 levels at 2 months on top of established risk factors and baseline BMP10 levels improved the C-indices for ischemic stroke/systemic embolism (from 0.73 to 0.75), heart failure hospitalization (0.76–0.77), and all-cause mortality (0.70–0.72), all P<0.05.

CONCLUSIONS: Elevated levels of BMP10 at 2 months strengthened the associations with the risk of ischemic stroke, hospitalization for heart failure, and all-cause mortality. Repeated measurements of BMP10 may further refine risk stratification in patients with AF.

Key Words: atrial fibrillation ■ biomarker ■ BMP10 ■ risk stratification ■ stroke

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CLINICAL PERSPECTIVE

What Is New?

- This study is the first to investigate the temporal changes of the novel biomarker BMP10 (bone morphogenic protein 10) over time in patients with atrial fibrillation.
- A repeated measurement of BMP10 after 2 months significantly strengthened the associations with the risk of ischemic stroke, hospitalization for heart failure, and all-cause mortality.

What Are the Clinical Implications?

- These findings suggest that incorporating repeated measurements of an atrial specific biomarker, BMP10, improves risk stratification for key AF-related adverse events.
- From a clinical perspective, this may guide more precise risk assessment and management strategies in patients with AF, potentially leading to more tailored interventions and improved patient outcomes.

Nonstandard Abbreviations and Acronyms

BMP10	bone morphogenetic protein 10
SE	systemic embolism

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia that is associated with an increased risk of stroke, heart failure (HF), and death.[1–4] The levels of cardiac biomarkers such as NT-proBNP (N-terminal pro-B-type natriuretic peptide) improve the prediction of adverse events in patients with AF.[5] The identification of novel biomarkers specifically related to atrial pathophysiology may offer a better understanding of the pathophysiology of AF and potentially aid clinicians in further improving the prognostication of major adverse cardiovascular events.[5,6] BMP10 (bone morphogenetic protein 10) has been established as a paired-like homeodomain 2 (*PITX2*)-repressed, atrial-specific biomarker involved in cardiac development and associated with the risk of ischemic stroke in patients with AF, and to a lesser degree hospitalization for HF and death.[6] However, the variability of BMP10 over time and the added value of repeated BMP10 measurement for risk stratification for these outcomes has not been previously studied.

The aims of the present study were to assess the BMP10 change over time, to elucidate the determinants influencing BMP10 level and its changes over time, and to evaluate the prognostic value of a repeated measurement of BMP10 regarding clinical outcomes in 2878 patients with AF on oral anticoagulation therapy in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

The ARISTOTLE trial (Clinicaltrials.gov ID: NCT00412984) recruited 18201 patients with AF and 1 or more clinical risk factors for ischemic stroke.[7,8] Patients were randomized 1:1 to apixaban or warfarin. The biomarker serial substudy aimed to include 5000 patients of whom 2878 had available plasma aliquots from blood samples obtained at baseline and after 2 months for determination of serial cardiac biomarker levels that is, BMP10, NT-proBNP, and cTnT (cardiac troponin). The participants of the present study exhibited representative baseline characteristics when compared with those included in the original ARISTOTLE biomarker substudy.[9] The median follow-up time from baseline was 1.8 years in this biomarker cohort. The trial and the biomarker substudy were approved by the appropriate ethics committees at all investigational sites and all patients provided written informed consent.

Outcomes

The primary outcome in the ARISTOTLE trial was stroke or systemic embolism (SE).[7,8] The present study investigated the association of a BMP10 measurement at 2 months and the subsequent outcomes of ischemic stroke or SE, hospitalization for HF, and all-cause mortality. In the ARISTOTLE trial, stroke was defined as a focal neurologic deficit, from a nontraumatic cause, lasting at least 24 hours and was categorized as ischemic (with or without hemorrhagic transformation), hemorrhagic, or of uncertain type. SE was defined as a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries), supported by evidence of embolism from surgical specimens, autopsy, angiography, or other objective testing. Deaths were classified as either cardiovascular or noncardiovascular. Outcomes were centrally adjudicated except hospitalization for HF, which was reported by the local investigator.

Biomarker Quantification

Blood was drawn from an antecubital vein into EDTA tubes and centrifuged within 2 hours of collection.

Plasma was aliquoted, frozen at −20 C, and within 1 week transferred to the long-term storage at −80 C until shipment to a central laboratory.

All plasma samples were analyzed at the Uppsala Clinical Research Center laboratory, Sweden. BMP10 was analyzed in plasma on an Elecsys e411 analyzer using a prototype Elecsys electrochemiluminescence immunoassay developed by Roche Diagnostics. The assay employs a quantitative sandwich principle, where the first monoclonal antibody specifically binds the BMP10 as a capture antibody and a ruthenylated second monoclonal antibody binds to BMP10 as a detection antibody. Recombinant BMP10 is used to normalize the measurements across the runs with a high degree of accuracy. The coefficient of variation was 6.0% and 4.3% for BMP10 concentrations of 1.39 and 3.56 ng/mL, respectively. NT-proBNP concentrations were analyzed in plasma by commercialized Elecsys electrochemiluminescence immunoassays (Roche Diagnostics) as previously published.[6]

Statistical Analysis

Baseline characteristics were presented by the biomarker quartile groups. The distribution of BMP10 was presented graphically by both a density and an empirical cumulative distribution function plot. The change of BMP10 from baseline to 2 months was tested using the Wilcoxon signed rank test.

Time to event was studied for ischemic stroke or SE, hospitalization for HF, and all-cause death. Follow-up was defined as the number of days from the 2-month sample until the respective event occurred or was censored for the event at the end of study or death. Incidence rates were estimated as the number of events divided by the total follow-up time with corresponding 95% CIs estimated using a gamma distribution. The median follow-up time, from 2 months to the end of study or death was estimated for each outcome by the Kaplan–Meier method while censoring for the event.

To assess the associations between 2-month BMP10 level and baseline variables, linear regression models with log-transformed BMP10 concentration at 2 months as outcome were used. Both univariable models, including each variable one at a time, and multivariable models, including all variables simultaneously were fitted. Continuous variables were entered as restricted cubic splines with 3 knots placed at the respective 10th, 50th, and 90th sample percentiles.

The coefficient of multiple determination was presented as a measure of the proportion of the total variance in the log-transformed biomarker that could be explained by the full set of variables in the model. The relative importance of each of the variables in the multivariable model was illustrated by plotting the partial coefficient of multiple determination for each variable. Models both with and without the baseline measurement of BMP10 were fitted. This makes it possible to evaluate the added value of the 2-month measurement when we already have a baseline measurement.

The cumulative event rates, estimated by the Kaplan–Meier method, were plotted for the arbitrary division of BMP10 into quarters for each outcome. Cox regression models were used to estimate unadjusted and adjusted associations between BMP10 and each outcome. To allow for nonlinear associations, the log-transformed BMP10 was represented as a restricted cubic spline with 3 knots placed at the respective 10th, 50th, and 90th sample percentiles of BMP10. For outcome, the different models that were fitted were Model 1: randomized treatment, age, sex, body mass index (BMI), current smoker, alcohol, type of AF, rhythm at baseline, heart failure, hypertension, diabetes, prior stroke/transient ischemic attack, prior peripheral artery disease, prior myocardial infarction, creatinine (baseline); and Model 2: Model 1 + NT-proBNP (month 2). Additionally, all outcome models were fitted including the BMP10 value at baseline. Because a nonlinear association was assumed, the full association cannot be summarized by a single hazard ratio (HR). Therefore, in the presentation of the results, the relative hazard of each event, with corresponding 95% CI, was presented as an arbitrary comparison between the third and the first sample quartile, representing the inner half of BMP10s distribution, thus providing an understanding of the differential risk of events associated with variations in the central range of BMP10 values. The full nonlinear association is presented graphically and the sample quartiles are indicated by vertical dashed lines. All analyses were conducted using R (version 4.2.1).

RESULTS

Baseline Characteristics and Demographics

Baseline characteristics are presented in Table. The median age of the patients was 70 years (interquartile range 63–76) and 63% were male. The median BMI was 28 kg/m^2, 83% had nonparoxysmal AF, 14% were in sinus rhythm at randomization, 31% had diagnosis of congestive HF, and 18% had previous stroke/transient ischemic attack (Table).

Temporal Dynamics and Distribution of BMP10

The median (25th–75th percentile) BMP10 concentration was 2.4 ng/mL (2.0–2.8) at baseline. At 2 months the median BMP10 concentration was significantly higher at 2.6 ng/mL (2.2–3.0). Examining BMP10

Table. Baseline Characteristics by BMP10 2-Month Quartile Group

Variable	BMP10 Q1	BMP10 Q2	BMP10 Q3	BMP10 Q4	Combined
Age, y	66.0 (59.0–72.0)	69.0 (62.0–75.0)	71.0 (65.0–77.0)	73.0 (67.0–78.0)	70.0 (63.0–76.0)
Sex, male	72.6% (521)	63.7% (467)	62.9% (451)	52.3% (371)	62.9% (1810)
Height (cm)	172.7 (165.0–179.0) [4]	170.0 (163.0–177.8) [4]	169.0 (161.0–176.0) [2]	164.0 (157.0–172.0) [1]	169.0 (161.0–177.0) [11]
Weight (kg)	89.0 (78.8–101.0)	84.0 (73.0–96.6)	81.2 (68.3–93.8)	71.9 (61.6–84.5)	82.0 (69.9–95.0)
Body mass index (kg/m^2)	29.9 (26.8–33.8)	29.1 (25.9–32.8)	28.0 (25.1–32.3)	26.4 (23.5–30.2)	28.4 (25.2–32.4)
Current smoker	9.3% (67) [0]	8.0% (59) [0]	8.7% (62) [1]	5.4% (38) [0]	7.9% (226) [1]
Randomized treatment: apixaban	55.4% (398)	52.4% (384)	48.3% (346)	48.9% (347)	51.3% (1475)
Type of AF: permanent/persistent	66.7% (478) [1]	82.0% (601) [0]	89.3% (640) [0]	94.9% (674) [0]	83.2% (2393) [1]
AF	64.6% (461) [4]	78.4% (573) [2]	86.3% (617) [2]	93.1% (660) [1]	80.6% (2311) [9]
Atrial flutter	4.8% (34) [7]	4.5% (33) [5]	4.1% (29) [6]	4.1% (29) [7]	4.4% (125) [25]
Sinus rhythm	28.7% (204) [8]	15.8% (115) [7]	9.0% (64) [6]	4.1% (29) [11]	14.5% (412) [32]
Paced rhythm	6.7% (47) [13]	5.8% (42) [9]	7.3% (52) [8]	6.0% (42) [14]	6.5% (183) [44]
Other rhythm	4.2% (27) [73]	2.9% (19) [83]	4.2% (27) [76]	5.0% (32) [73]	4.1% (105) [305]
Rhythm (% AF)	68.2% (486) [5]	82.5% (602) [3]	90.2% (645) [2]	96.2% (683) [0]	84.2% (2416) [10]
Heart failure	34.0% (244)	28.9% (212)	29.7% (213)	33.0% (234)	31.4% (903)
Hypertension	88.6% (636)	88.1% (646)	84.1% (603)	85.9% (610)	86.7% (2495)
Diabetes	22.8% (164)	24.4% (179)	25.2% (181)	24.9% (177)	24.4% (701)
Prior stroke/transient ischemic attack	17.8% (128)	17.1% (125)	18.4% (132)	19.4% (138)	18.2% (523)
Prior bleeding	13.4% (96)	17.7% (130)	16.7% (120)	22.4% (159)	17.5% (505)
Prior peripheral artery disease	4.2% (30)	3.5% (26)	4.6% (33)	5.4% (38)	4.4% (127)
Vascular disease	24.7% (177)	25.1% (184)	23.3% (167)	26.5% (188)	24.9% (716)
Prior myocardial infarction	13.6% (98)	12.4% (91)	12.1% (87)	14.9% (106)	13.3% (382)
Cystatin C (mg/L)	0.9 (0.8–1.1) [1]	0.9 (0.8–1.1) [1]	1.0 (0.8–1.2) [2]	1.1 (0.8–1.3) [0]	1.0 (0.8–1.2) [4]
Creatinine (μmol/L)	84.9 (76.0–99.9)	88.4 (76.9–101.7)	90.2 (76.0–106.1)	91.1 (76.9–111.4)	88.4 (76.0–104.3)
BMP10 baseline (ng/mL)	1.9 (1.7–2.2) [1]	2.3 (2.0–2.5) [0]	2.6 (2.3–2.8) [0]	3.0 (2.7–3.4) [1]	2.4 (2.0–2.8) [2]

m (a–b) represents median (Q1–Q3).
p% (n) represent percentage (frequency). Percentages computed by group. [M] represents number of patients with missing data.
AF indicates atrial fibrillation; and BMP10, bone morphogenic protein 10.

concentrations after 2 months, 68% (1966) participants exhibited higher levels, and 31% (880) participants demonstrated a decrease. The median increase of BMP10 between baseline and 2 months was 7.8% (P<0.001). The distribution of and agreements between BMP10 concentration at baseline and after 2 months are shown in Figures 1A and 1B.

Determinants of Increased Levels of BMP10 at Follow-Up

In the multivariable model, the baseline characteristics most strongly associated with higher BMP10 levels at 2 months in descending level of importance were lower BMI, female sex, impaired kidney function, older age, AF rhythm, diabetes, and randomized treatment with warfarin as compared with apixaban (Figure 2A). In the model also containing the baseline level of BMP10, the baseline BMP10 level was the factor most strongly associated with higher BMP10 levels at 2 months (Figure 2B), followed by the previously listed variables. When adjusted for baseline BMP10 levels, patients randomized to warfarin had 2.2% higher BMP10 levels at 2-month follow-up as compared with those randomized to apixaban (P<0.001).

Repeated BMP10 Measurement and Association With Outcomes

During the median follow-up period of 1.8 years, after the 2-month visit, there was a total (incidence rate per 100 person-years) of 34 (0.65) ischemic stroke/SE, 99 (1.89) hospitalizations for HF, and 155 (2.91) all-cause deaths. Kaplan–Meier estimates of cumulative event rates by quartile groups of BMP10 at 2 months are presented in Figure 3.

For the outcome ischemic stroke/SE, Cox-regression models adjusted for baseline BMP10 levels, randomized treatment, creatinine, and other clinical variables (Model 1), comparing the third and first sample quartiles, showed an HR of 1.33 (95% CI, 0.67–2.63, P=0.037). The risk increased with higher

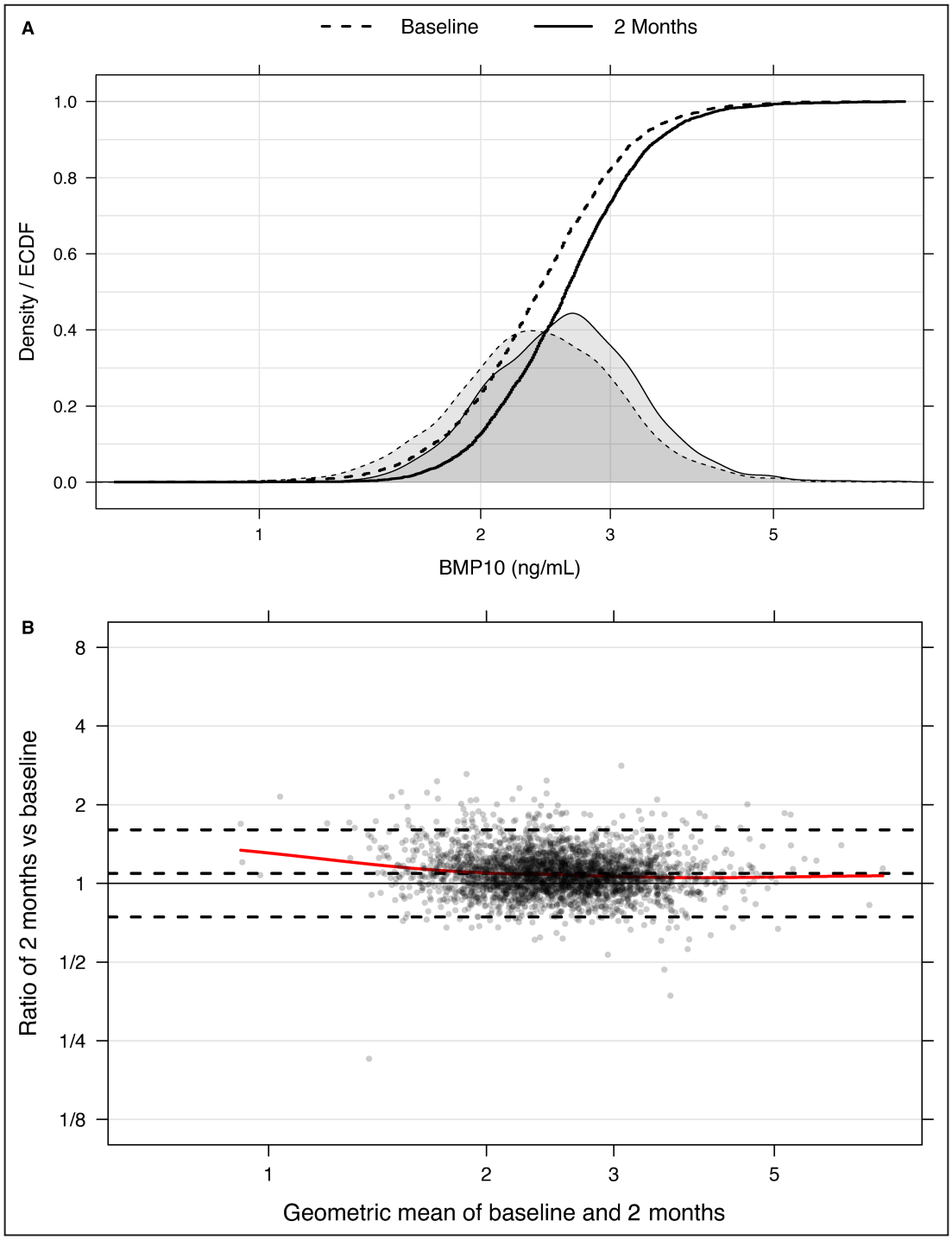

Figure 1. BMP10 concentration at baseline and 2 months.
A, Distribution of BMP10 at baseline (dashed line) and at 2 months (solid line). The shaded area represents the density and the lines the empirical cumulative distribution function (ECDF). **B**, Bland–Altman plot of the ratio of the 2 months to baseline measurement in relation to the geometric mean of the 2-month measurement. The dashed lines indicate the mean and 2 SDs distance from the mean. The red line indicates a less smooth scatterplot line. BMP10 indicates bone morphogenic protein 10.

BMP10 levels in a nonlinear fashion (Figure 3). The association of BMP10 with ischemic stroke/SE was slightly attenuated after extending the multivariable adjustment to also include the cardiac biomarker NT-proBNP (model 2), HR 1.25 (95% CI, 0.63–2.50, P=0.056) (Figure 4).

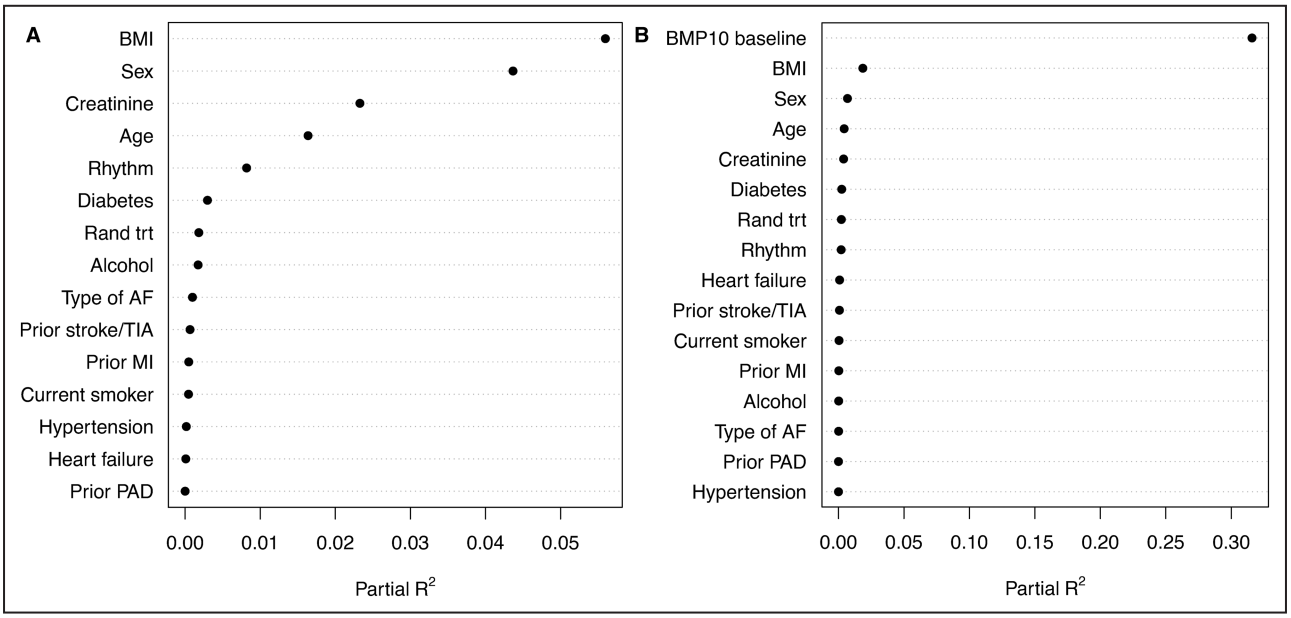

Figure 2. Variable importance of BMP10 at 2 months.
Contribution of BMP10 at 2 months (**A**) in the multivariable model not including BMP10 baseline, R^2 overall=0.24, and (**B**) in the multivariable model including BMP10 baseline, R^2 overall=0.56. AF indicates atrial fibrillation; BMI, body mass index; BMP10, bone morphogenic protein 10; MI, myocardial infarction; PAD, peripheral arterial disease; R^2, coefficient of multiple determination; Rand trt, randomized treatment; and TIA, transient ischemic attack.

For the outcome hospitalization for HF, Cox-regression models adjusted for model 1, comparing the third and first sample quartiles, the HR was 1.91 (95% CI, 1.17–3.12, *P*<0.012). The risk increased linearly with higher BMP10 levels at 2 months (Figure 3). The association with hospitalization for HF was no longer statistically significant after extending the multivariable adjustment to include NT-proBNP (Model 2, HR, 1.31 [95% CI, 0.85–2.30], *P*=0.305) (Figure 4).

For the outcome of all-cause mortality, Cox-regression models adjusted for model 1 comparing the third and first sample quartiles, the HR was 1.61 (95% CI, 1.17–2.21, *P*<0.001). The risk increased nonlinearly with higher BMP10 (Figure 3). After extending the multivariable adjustment to include NT-proBNP (model 2) the result remained statistically significant (HR, 1.16 [95% CI, 0.85–1.59], *P*=0.009) (Figure 4).

Discriminatory Value of Repeated BMP10 Measurement

Addition of the repeated BMP10 measurement on top of established risk factors and the baseline level of BMP10 (Model 1) improved the prognostication for ischemic stroke/SE with C index increasing from 0.73 (95% CI, 0.64–0.82) to 0.75 (95% CI, 0.65–0.84, *P*=0.037). Similarly, repeated measurement of BMP10 at 2 months improved the C index regarding hospitalization for HF from 0.76 (95% CI, 0.70–0.80) to 0.77 (95% CI, 0.73–0.82, *P*=0.01), and for all-cause mortality from 0.70 (95% CI, 0.66–0.74) to 0.72 (95% CI, 0.68–0.76, *P*<0.001).

DISCUSSION

The main findings of the present follow-up study after 2-month randomized anticoagulation treatment were that (1) BMP10 increased approximately 7.8% over 2 months; (2) assignment to warfarin compared with apixaban treatment was associated with higher BMP10 levels; (3) higher BMP10 levels at 2 months were associated with higher BMP10 levels at baseline and still the same clinical variables as at baseline (ie, lower BMI, female sex, kidney dysfunction, and older age); and (4) higher BMP10 levels during repeated measurement were significantly associated with an increased risk of ischemic stroke/SE, HF hospitalization, and all-cause death.

To our knowledge, this is the first study to evaluate the added value of repeated assessment of BMP10 for risk stratification in anticoagulated patients with AF. The analyses were adjusted for commonly available variables such as age, prior stroke/transient ischemic attack, and the clinical biomarker NT-proBNP known to be independent and powerful predictors of adverse events in patients with AF.[4,10]

Repeated measurements of cardiovascular biomarkers reflecting cardiac stress and dysfunction such as cTnT and NT-proBNP have been previously reported

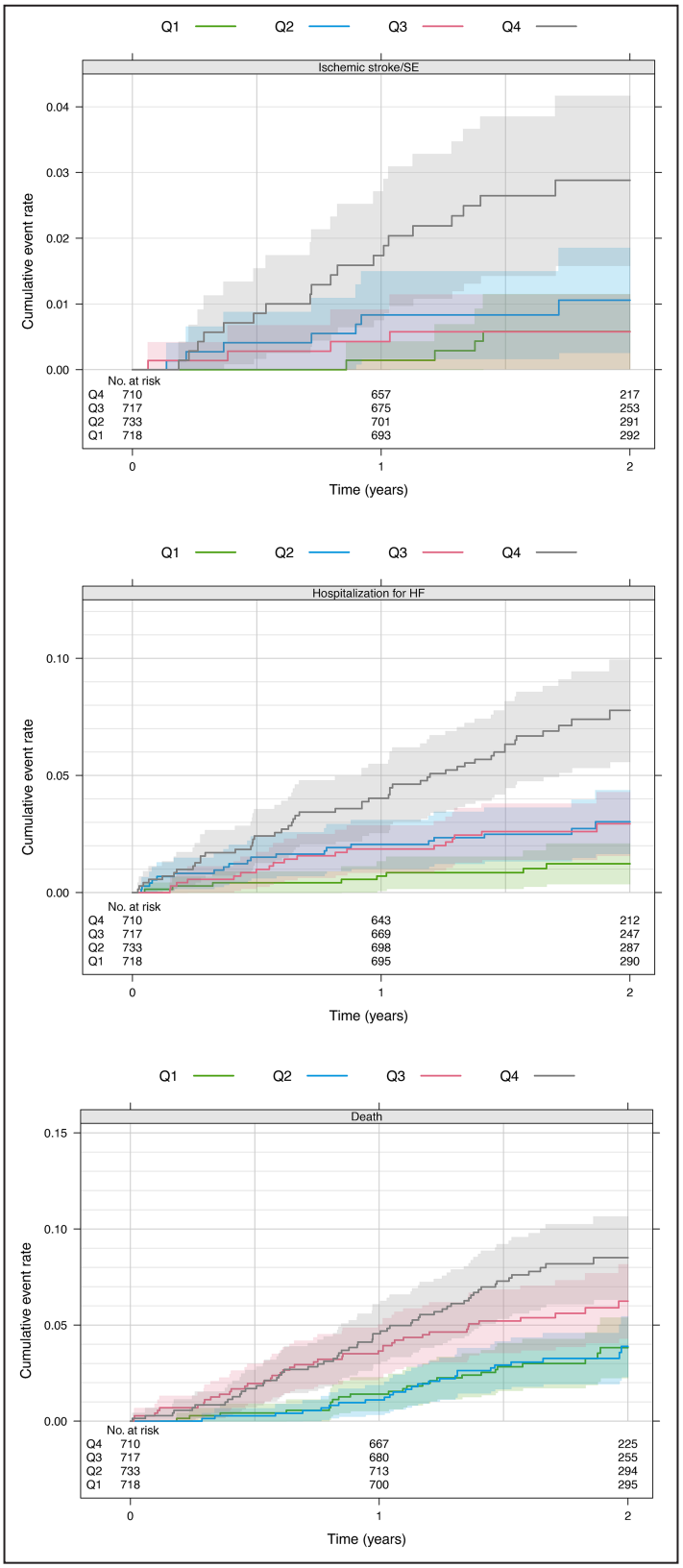

Figure 3. Kaplan Meier curves of the cumulative event rate of ischemic stroke and systemic embolism, hospitalization for heart failure, and all-cause mortality by BMP10 quartile group at 2 months. BMP10 indicates bone morphogenic protein 10; HF, heart failure; and SE, systemic embolism.

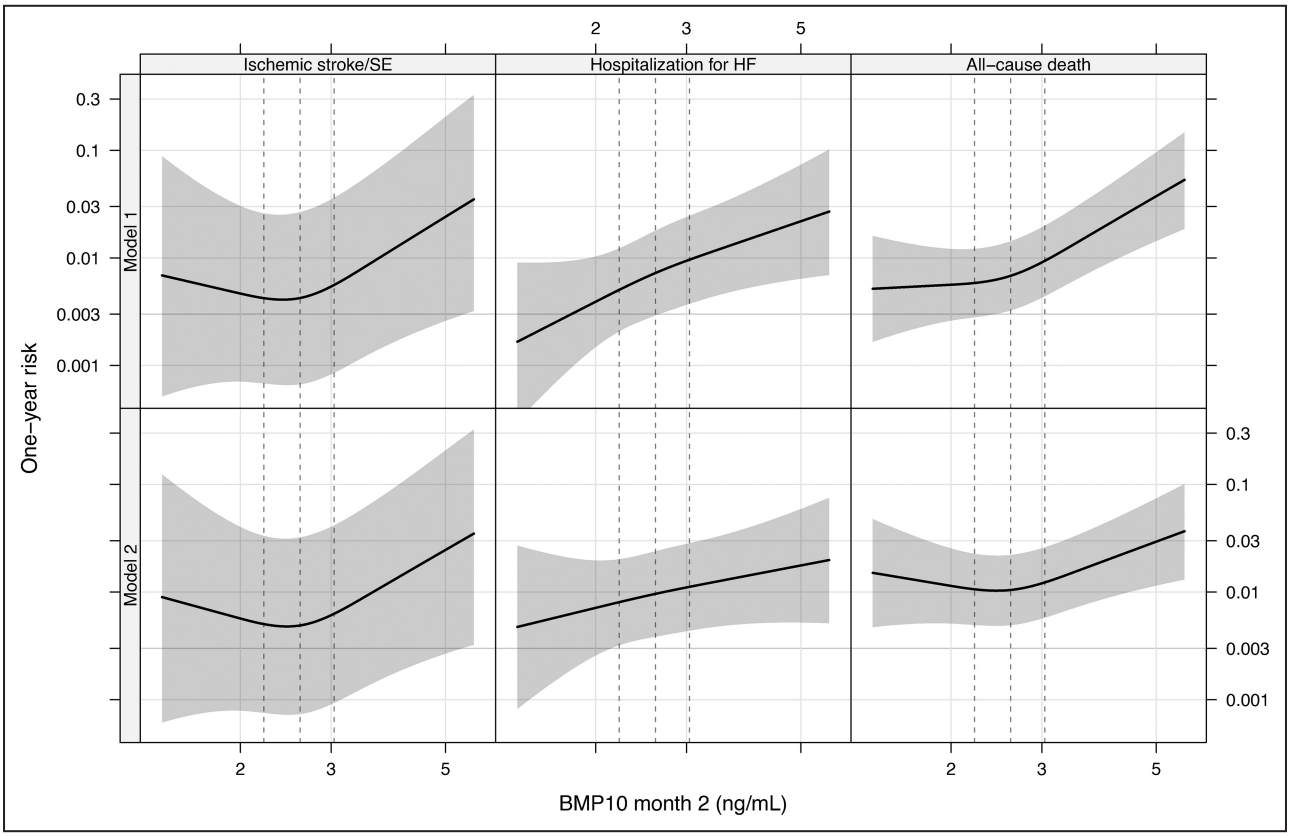

Figure 4. Predicted event rates for the outcomes of ischemic stroke and systemic embolism, hospitalization for heart failure, and all-cause death.
Model 1 is presented in the upper part of the figure adjusted for BMP10 baseline, the variables of the CHA_2DS_2–VASc score, serum creatinine, randomized treatment, body mass index, smoking status, atrial fibrillation type, and rhythm upon inclusion; Model 2 is presented in the lower part of the figure adjusted for variables included in Model 1 + NT-proBNP (N-terminal prohormone of brain natriuretic peptide). The vertical dashed lines indicate the 3 sample quartiles. BMP10 indicates bone morphogenic protein 10; HF, heart failure; and SE, systemic embolism.

to improve prognostication of cardiovascular events and mortality in patients with AF. We recently, for the first time, presented the robust associations between BMP10 and ischemic stroke and hospitalization for HF from 2974 patients managed without oral anticoagulation treatment in the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial and from 13 709 patients treated with oral anticoagulation in the ARISTOTLE trial.[5,11] For ischemic stroke/SE the results in the present study showed a consistent and significant association in patients with repeated BMP10 measurement. Furthermore, similar to this study, recent data also suggest an association between BMP10 and all-cause mortality.[6,12] A repeated BMP10 measurement provided a modest but statistically significant increase in risk discrimination. The application of these findings in clinical context would be that BMP10 should be measured as close to the point of evaluation as possible, because a 2-month interval is relatively short for repeated assessment in routine practice. Additional longitudinal studies of the long-term dynamics would therefore be valuable.

Previous studies, in line with our findings have reported similar BMP10 concentrations as well as similar positive associations between higher BMP10 concentrations and older age, female sex, lower BMI, renal failure, and nonparoxysmal AF. These findings align with previous observations indicating that higher BMP10 levels are associated with AF rhythm as well as with AF recurrence after AF ablation, that lower BMI is paradoxically associated with higher stroke risk (the "obesity paradox") in AF, and lastly with the inconsistent association between female sex and its relation to ischemic stroke risk.[11–16]

Comparing the performance of BMP10 with other established cardiovascular biomarkers, such as NT-proBNP, revealed valuable insights. Although quantification of BMP10 levels at 2 months demonstrated significant prognostic value for ischemic stroke, death, and HF hospitalization, its association with HF hospitalization became nonsignificant after adjusting for NT-proBNP. This suggests that BMP10 may provide

added information on top of NT-proBNP for specific outcomes, potentially reflecting differences in the pathophysiological mechanisms between these 2 biomarkers and thus reinforcing the concept of the atrial specificity of BMP10.

A novel finding in this ARISTOTLE biomarker cohort study was that patients assigned to receive apixaban had 2.2% (P<0.001) lower BMP10 concentrations at 2 months as compared with patients assigned to warfarin. The exact mechanism underlying this observation remains uncertain, and it may even be due to chance. However, a potential explanation may be through a link between vitamin-K antagonists, BMP10, and inflammation. Cell experiments have suggested that BMP may be involved in endothelial inflammation and is upregulated in an inflammatory milieu.[13] Inflammatory activity, measured with interleukin 6, has previously been shown to be higher in patients with AF treated with warfarin as compared with apixaban.[14] Further, evidence from animal experiments and clinical and epidemiological data suggest that long-term treatment with warfarin, but not with novel direct oral anticoagulants, increases the risk of, and may even induce, vascular calcification in individuals.[15–17] Pathological activation of the vascular endothelium is known to play a central role in chronic systemic inflammation, which is the basis of many cardiovascular, rheumatological, and respiratory diseases. Considering these factors, this might provide a hypothesis regarding higher BMP10 levels in patients with AF treated with vitamin-K antagonists possibly explaining this small but statistically significant difference in mean BMP10 concentration between the randomized treatment arms. It is also possible that an agent more effective at preventing stroke and bleeding might result in lower levels of a stress marker due to preventing these events that cause stress.

Limitations and Strengths

This study is the first and largest study to evaluate serial measurements of BMP10 and its relation to clinical outcomes. Strengths of this study include the analyses of a closely monitored large randomized trial cohort in which outcomes were systematically adjudicated on the basis of prespecified criteria by a clinical events committee whose members were unaware of study group assignments. Confounding factors were minimized by adjusting for a wide range of established clinical risk factors. The assessment of the biomarker relied on precise measurements of BMP10 using a novel prototype assay from Roche Diagnostics. One of the limitations is that this was a clinical trial cohort of patients with AF on oral anticoagulation with increased stroke risk and as a result, it is uncertain whether the findings can be generalized and extended to individuals with AF and a lower risk of stroke. Although the present study provides insights into the relationship between BMP10 and adverse outcomes in patients with AF, it is essential to acknowledge the imperative for external validation to examine the generalizability of our findings.

CONCLUSIONS

In anticoagulated patients with AF, the median level of BMP10 increased by 7.8% during 2 months. A higher BMP10 level was associated with a higher BMP10 level at baseline and with lower BMI, female sex, impaired kidney function, older age, AF rhythm, diabetes, and treatment with warfarin as compared with apixaban. A further increased level of the atrial biomarker BMP10 at 2 months strengthened the associations with the risk of ischemic stroke, hospitalization for HF, and all-cause mortality. Repeated measurements of BMP10 may further refine risk stratification in patients with AF.

ARTICLE INFORMATION

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Disclosures

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