Low Body Weight Is Associated With the Incidence of Stroke in Atrial Fibrillation Patients – Insight From the Fushimi AF Registry –

Yasuhiro Hamatani, MD; Hisashi Ogawa, MD; Ryuji Uozumi, BSc; Moritake Iguchi, MD, PhD; Yugo Yamashita, MD; Masahiro Esato, MD, PhD; Yeong-Hwa Chun, MD, PhD; Hikari Tsuji, MD, PhD; Hiromichi Wada, MD, PhD; Koji Hasegawa, MD, PhD; Mitsuru Abe, MD, PhD; Satoshi Morita, PhD; Masaharu Akao, MD, PhD

Background: Japanese patients with atrial fibrillation (AF) are generally small and lean, but knowledge of the clinical characteristics of those with low body weight (LBW: ≤50 kg) is limited.

Methods and Results: The Fushimi AF Registry is a community-based prospective survey of AF patients who visited the participating medical institutions in Fushimi-ku, Japan. The BW and follow-up data were available for 2,945 patients. We compared the background and the incidence of clinical events during a median follow-up of 746 days between a LBW and non-LBW group. Patients in the LBW group accounted for 26.8% (788 patients) of the total. The LBW group was more often female, older, and had higher CHADS2 score. The incidence of stroke/systemic embolism (SE) during follow-up was higher in the LBW group (hazard ratio (HR): 2.19, 95% confidence interval (CI): 1.57–3.04; \(P<0.01\)), whereas that of major bleeding was comparable (HR: 1.05, 95% CI: 0.64–1.68; \(P=0.84\)). This trend was consistently observed in the subgroups stratified by age, sex, and oral anticoagulant prescription at baseline. Multivariate analysis as well as propensity-score matching analysis further supported the significance of LBW as a risk of stroke/SE.

Conclusions: Patients in the LBW group had high risk profiles and showed a higher incidence of stroke/SE, but the incidence of major bleeding was not particularly high. (Circ J 2015; 79: 1009–1017)

Key Words: Atrial fibrillation; Low body weight; Stroke

trial fibrillation (AF) is a common cardiac arrhythmia among the elderly, and its incidence is increasing significantly (0.6% of the total population in Japan). AF increases the risk of thromboembolism, such as stroke or systemic embolism (SE), 5-fold. Oral anticoagulants (OAC) are highly effective therapy for preventing thromboembolism in AF patients and for many years, warfarin was the only OAC for preventing thromboembolism, but novel OACs (NOACs) have recently become available in clinical practice. There have been several studies investigating the effect of obesity on stroke/SE in patients with non-valvular AF, but that of low body weight (LBW) has not been reported. Large clinical trials of NOACs demonstrated that bleeding complications were more often observed in patients with LBW, especially if ≤50kg. However, those studies were performed mainly in Western populations, whereas Japanese are generally small and lean, and data regarding those with LBW are very limited.

The Fushimi AF Registry is a community-based prospective survey of AF patients in Fushimi-ku, Japan. We aimed to enroll all AF patients who visited the participating medical institutions. The aim of this study was to evaluate the effect of LBW on AF outcomes, such as stroke, SE, and major bleeding, in Japanese AF patients, based on the outcomes recorded in the Fushimi AF Registry.
Methods

The detailed study design, patient enrollment, the definition of the measurements, and subjects’ baseline clinical characteristics in the Fushimi AF Registry were previously described (UMIN Clinical Trials Registry: UMIN000005834). The inclusion criterion for the registry is the documentation of AF on 12-lead ECG or Holter monitoring at any time. There are no exclusion criteria. A total of 79 institutions, all of which are members of Pushimi-Ishikai (Pushimi Medical Association), participated in the registry. The participating institutions comprised 2 cardiovascular centers (National Hospital Organization Kyoto Medical Center and Ijinkai Takeda Hospital), 9 small- and medium-sized hospitals, and 68 primary care clinics. The enrollment of patients was started in March 2011. All of the participating institutions attempted to enroll all consecutive patients with AF under regular outpatient care or under admission. Clinical data of the patients were registered in the Internet Database System (https://edmstweb16.epsc.s.is.jp/edmstweb/002001/FAF/top.html) by the doctors in charge at each institution. Data were automatically checked for missing or contradictory entries and values out of the normal range. Additional editing checks were performed by clinical research coordinators at the general office of the registry. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethics committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital.

BW was recorded to the nearest 100 g and the data were collected at the time of entry into the registry. We defined LBW as ≤50 kg. We Compared the background and the incidence of clinical events during the follow-up period between the LBW group and non-LBW group. We excluded registry participants for whom BW data were missing.

The primary endpoint in the analysis was the incidence of stroke/SE during the follow-up period. Other clinical endpoints included the incidence of major bleeding, all-cause death, and a composite endpoint of ‘stroke, SE, and all-cause death’ during the follow-up period. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery. SE was defined as an acute vascular occlusion of an extremity or organ. Major bleeding was defined as a reduction in the hemoglobin level of ≥2 g/dl, transfusion of ≥2 units of blood, or symptomatic bleeding in a critical area or organ. OACs included warfarin, dabigatran, rivaroxaban, and apixaban. The prothrombin time-international normalized ratio (PT-INR) data were collected at the time of enrollment. The therapeutic range of PT-INR was stratified into 3 groups (over, optimal, and under) according to the current enrollment. The therapeutic range of PT-INR was stratified into normalized ratio (PT-INR) data were collected at the time of enrollment. The therapeutic range of PT-INR was stratified into 3 groups (over, optimal, and under) according to the current Japanese guidelines. The Japanese guidelines set different target PT-INR ranges for patients taking warfarin: 1.6–2.6 for elderly patients (≥70 years old) and 2.0–3.0 for younger patients (<70 years old).

Statistical Analysis

Continuous variables are expressed as mean±standard deviation (SD), or median and interquartile range. Categorical variables are presented as numbers and percentages. We compared categorical variables using the chi-square test when appropriate; otherwise, we used Fisher’s exact test. We compared continuous variables using Student’s t-test on the basis of the distribution. Data were analyzed as crude and stratified by OAC prescription at baseline because this variable was considered to be a confounder. Data were also stratified by age (≥75 vs. <75 years) and sex because men and women or the young and the old might have differing body composition. The Kaplan-Meier method was used to estimate the cumulative incidence of each clinical event. We carried out multivariate analysis using a Cox proportional hazards model. The covariates chosen to be included in model 1 were LBW, components of the CHADS 2 risk score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke), and OAC prescription at baseline. Those in model 2 were the covariates included in model 1: female sex, vascular disease, and renal dysfunction (creatinine clearance <60 ml/min) according to the components of the CHADS 2-VASc risk score and R:CHADS 2 risk score. To reduce the effect of potential confounding in this observational study, we used propensity-score matching to perform rigorous adjustment for the differences in the baseline characteristics. The covariates entered into the propensity score were OAC prescription at baseline, the components of the CHADS 2-VASc risk score, and clinically relevant factors (paroxysmal AF, chronic kidney disease, anemia (defined as hemoglobin <11 g/dl), chronic obstructive pulmonary disease, and smoking history). The propensity score-matched pairs were created by matching the LBW and non-LBW groups on the basis of the nearest neighbor pair-matching algorithm with a 0.3 caliper width using R version 3.1.0 (package ‘Matching’ version 4.8-3.4, http://cran.r-project.org/web/packages/Matching/index.html). A matching ratio of 1:1 was used. The incidences of stroke/SE were compared between the LBW and non-LBW groups after matching. Thereafter, we performed similar tests for the composite endpoint of ‘stroke, SE, and all-cause death’. We used JMP version 9 (SAS Institute, Cary, NC, USA) to perform all of these analyses except propensity-score matching. Two-sided P-values less than 0.05 were considered statistically significant.

Results

A total of 4,115 patients had been enrolled by the end of July 2014. Of 3,666 patients who were enrolled 1 year prior (by the end of July 2013), follow-up data (collected every year) were available for 3,304 patients (follow-up rate: 90.1%). Among these 3,304 patients, BW data were available for 2,945 patients, and 359 patients’ BW data were missing. Patients without BW data were younger, had lower CHADS 2 score (patients without BW data vs. those with BW data; mean age 72.0 vs. 73.8 years; P<0.01, and mean CHADS 2 score 1.54 vs. 2.09; P<0.01), and lower cumulative incidence of stroke during the follow-up period (1.7% (6/359 patients) vs. 5.0% (148/2,945 patients); P<0.01).

A total of 2,945 patients were included in the analysis. Median follow-up period was 746 days (interquartile range: 404–1,109 days). The distributions of BW in the entire cohort, in male patients, and in female patients are shown in Figure 1. The mean (±SD) body weight was 59.1 (±13.3) kg in the entire cohort. Patients in the LBW group accounted for 26.8% (788 patients) of all of the patients, and 47.0% (433 patients) of patients ≥80 years of age. Those with BW ≤60 kg accounted for 55.1% (1,623 patients) of all of the patients. The mean (±SD) BW was 64.6 (±11.9) kg in males and 50.9 (±11.0) kg in females.

Baseline characteristics, comorbidities, and OAC prescription at baseline are shown in Table 1. The LBW group was more often female (LBW group 78% vs. non-LBW group 26%; P<0.01) and older (79.6±9.8 vs. 71.8±10.2 years; P<0.01). The mean CHADS 2 score was higher in the LBW group (2.31±1.33 vs. 2.00±1.32; P<0.01), and histories of stroke and heart failure were more common in the LBW group (22% vs.
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17%, P<0.01; and 39% vs. 25%, P<0.01, respectively), whereas hypertension and diabetes mellitus were less common (57% vs. 65%, P<0.01; and 15% vs. 28%, P<0.01, respectively, LBW vs. non-LBW). The LBW group tended to experience more episodes of major bleeding (4% vs. 2%, P=0.04). The LBW group received a prescription of OAC less often at baseline (46% vs. 56%, P<0.01). The details of the prescribed OACs are as follows: warfarin: 44% vs. 51% (P<0.01), dabigatran: 2% vs. 4% (P<0.01), rivaroxaban: 0.4% vs. 0.8% (P=0.20), and apixaban: 0.1% vs. 0.1% (P=0.80), respectively. The intensity of warfarin control was comparable between the LBW and non-LBW groups.

The incidences of major clinical events in the entire cohort during follow-up period were as follows: stroke/SE in 148 (2.5 per 100 person-years), ischemic stroke in 111 (1.9 per 100 person-years), hemorrhagic stroke in 34 (0.6 per 100 person-years), SE in 3, major bleeding in 89 (1.5 per 100 person-years), non-cardiac death in 346 (5.7 per 100 person-years), and stroke/SE/all-cause death in 516 (8.7 per 100 person-years). Annual incidence of stroke/SE, major bleeding, all-cause death, and stroke/SE/all-cause death in the LBW group were 4.3 per 100 person-years, 1.6 per 100 person-years, 13.5 per 100 person-years, and 16.1 per 100 person-years, respectively (Table 2).

Kaplan-Meier curves for the incidences of stroke/SE, major bleeding, all-cause death, and stroke/SE/all-cause death are shown in Figure 2. LBW was significantly associated with a higher incidence of stroke/SE (hazard ratio (HR): 2.19, 95% confidence interval (CI): 1.57–3.04, P<0.01), worse mortality rate (HR: 2.74, 95% CI: 2.25–3.32, P<0.01), and higher incidence of stroke/SE/all-cause death (HR: 2.45, 95% CI: 2.06–2.92, P<0.01), compared with non-LBW. The incidence of major bleeding was comparable between the groups (HR: 0.64–1.68, P=0.84).

A higher risk of stroke/SE during follow-up period in the LBW group was consistently observed in patients stratified by OAC prescription at baseline (with OAC: HR: 1.94, 95% CI: 1.23–2.98, P<0.01; without OAC: HR: 2.65, 95% CI: 1.59–4.40, P<0.01), by sex (male: HR: 2.79, 95% CI: 1.56–4.68, P<0.01; female: HR: 2.46, 95% CI: 1.46–4.32, P<0.01), or by age (≥75 years: HR: 1.80, 95% CI: 1.23–2.65, P<0.01; <75 years: HR: 1.86, 95% CI: 0.87–3.63, P=0.08) (Figure 3). Statistical test for interaction was not significant for all subgroups (P=0.28 for interaction with OAC prescription, P=0.78 for that with sex, and P=0.93 for that with age). The incidence of major bleeding during the follow-up period was consistently comparable between the groups stratified by OAC prescription at baseline (with OAC: HR: 0.68, 95% CI: 0.30–1.37, P=0.30; without OAC: HR: 1.67, 95% CI: 0.81–3.07, P=0.17), by sex (male: HR: 1.49, 95% CI: 0.62–3.06, P=0.34; female: HR: 1.67, 95% CI: 0.74–3.97, P=0.22) or by age (≥75 years: HR: 1.07, 95% CI: 0.60–1.84, P=0.83; <75 years: HR: 0.59, 95% CI: 0.14–1.64, P=0.34).

Figure 1. Distribution of body weight in (A) the entire cohort, (B) male patients and (C) female patients.
In the multivariate analysis, after adjustment for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke, and OAC prescription at baseline (model 1), LBW was an independent risk factor of the incidence of stroke/SE during the follow-up period (HR: 1.84, 95% CI: 1.29–2.60, P<0.01). Even after adjustment by the covariates included in model 1 plus vascular disease, female sex, and renal dysfunction (model 2), LBW remained an independent risk factor of stroke/SE (HR: 2.13, 95% CI: 1.39–3.27, P<0.01) (Table 3).

Propensity score-matching for the entire cohort yielded 538 matched pairs of patients. In the matched cohort, there were no longer any significant differences between the LBW and non-LBW groups for any covariate. The cumulative events and incidence of stroke/SE in the propensity score-matched cohort during the follow-up period was 59 (2.8 per 100 person-years). Annual incidence of stroke/SE in LBW group was 3.9 per 100 person-years (Table 4). For the 538 propensity score-matched pairs, LBW was significantly associated with a higher incidence of stroke/SE (HR: 2.13, 95% CI: 1.39–3.27, P<0.01) (Figure 4).

In addition, LBW was significantly associated with a higher incidence of the composite endpoint of ‘stroke, SE, and all-cause death’. It was also the case in the subgroups stratified by age, sex, and OAC prescription at baseline, or in the propensity score-matched cohort. This excludes the possibility that undiagnosed stroke was much more frequent in the non-LBW group.

We also investigated the possibility of a J-curve or U-shaped relationship between BW and thromboembolism. Patients with high BW (>60 kg, >70 kg, >80 kg, and >90 kg) were not high risk for thromboembolism in either the univariate or multivariate analysis.

### Discussion

**BW and the Risk of Stroke**

To the best of our knowledge, the effect of LBW on AF outcomes has not been reported. Japanese patients are generally small and lean, and their mean BW is much lower than that of Western populations. The Fushimi AF Registry represents the current status of “real-world” AF patients in Japan, and contains many frail elderly patients with LBW.

A previous study concluded that overweight patients with...
AF patients with low body weight in older patients with hypertension was associated with increased risk of death and stroke, and underweight patients with acute stroke had a higher risk of stroke recurrence. The mechanisms by which LBW is associated with a higher risk of stroke/SE are unknown, but there are various possible explanations. First, LBW may be simply the consequence of poor nutritional status, or illness-related weight loss because of malignancy, chronic obstructive pulmonary disease, etc. Second, other studies found that being overweight was associated with a significantly lower risk of all-cause mortality, and concluded that there might be an obesity paradox among AF patients. These studies excluded underweight patients with a body mass index <18.5, and the characteristics of underweight patients with AF are unknown. There have been a couple of studies showing a relationship between underweight and stroke in non-AF patients: low body mass index in older patients with hypertension was associated with increased risk of death and stroke, and underweight patients with acute stroke had a higher risk of stroke recurrence. The mechanisms by which LBW is associated with a higher risk of stroke/SE are unknown, but there are various possible explanations. First, LBW may be simply the consequence of poor nutritional status, or illness-related weight loss because of malignancy, chronic obstructive pulmonary disease, etc. Second,
overweight patients have a higher prevalence of coexisting conditions such as hypertension, dyslipidemia, and diabetes mellitus, and they may be more likely to receive treatment for such comorbidities than LBW patients.²² However, the higher risk of stroke/SE in the present LBW group from the Fushimi AF Registry patients persisted after adjustment for sex, age, CHADS² score, and OAC prescription, and also persisted after adjustment for antihypertensive agents, lipid-lowering agents, oral hypoglycemic agents, and insulin. Third, underweight patients may have advanced atrial fibrosis and remodeling through activation of the renin-angiotensin system.²³ Lean patients have shown greater increases in plasma renin levels than obese patients during stress testing.²⁴ Fourth, low body mass index is reportedly associated with impaired endothelial dysfunction, leading to reduced bioavailability of nitric oxide, which plays a role in the regulation of vascular tone and inhibi-

**Figure 3.** Kaplan-Meier curves for the incidence of stroke or systemic embolism (SE) in various subgroups during follow-up period. We stratified the entire cohort by oral anticoagulant (OAC) prescription at baseline (with OAC vs. without OAC), by sex (male vs. female), and by baseline age (≥75 vs. <75 years); CI, confidence interval; HR, hazard ratio; LBW, low body weight.
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BW and the Risk of Bleeding

Bleeding complications with NOACs in LBW patients have been reported. In the RE-LY trial of dabigatran, bleeding complications were more often observed in those with a LBW (≤50 kg).12 In the J-ROCKET trial, which compared rivaroxaban with warfarin for the prevention of stroke in Japanese AF patients, the rate of bleeding complications was also higher in those with a LBW (≤50 kg).30 Increased bleeding complications among the present LBW patients were consistent with results.

Table 3. Indicators of the Incidence of Stroke or Systemic Embolism During Follow-up of AF Patients From the Fushimi AF Registry – Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>LBW</td>
<td>1.84 (1.29–2.60)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>OAC prescription at baseline</td>
<td>1.08 (0.77–1.52)</td>
<td>0.65</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.14 (0.80–1.61)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.03 (0.74–1.46)</td>
<td>0.86</td>
</tr>
<tr>
<td>Age (≥75 years)</td>
<td>1.96 (1.36–2.85)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.25 (0.85–1.79)</td>
<td>0.25</td>
</tr>
<tr>
<td>History of stroke</td>
<td>1.90 (1.32–2.68)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female sex</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>–</td>
<td>–</td>
</tr>
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Table 4. Propensity Score-Matched Cohort of AF Patients From the Fushimi AF Registry, Baseline Characteristics and Incidence of Clinical Events During Follow-up

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>LBW (n=538)</th>
<th>Non-LBW (n=538)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>368 (68%)</td>
<td>373 (69%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>350 (65%)</td>
<td>353 (66%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>277 (51%)</td>
<td>267 (50%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Smoking history</td>
<td>129 (24%)</td>
<td>113 (21%)</td>
<td>0.38</td>
</tr>
<tr>
<td>History of stroke</td>
<td>120 (22%)</td>
<td>114 (21%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Heart failure</td>
<td>171 (32%)</td>
<td>171 (32%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>324 (60%)</td>
<td>325 (60%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>99 (18%)</td>
<td>91 (17%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>57 (11%)</td>
<td>57 (11%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>216 (40%)</td>
<td>212 (39%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Anemia (hemoglobin &lt;11 g/dl)</td>
<td>139 (26%)</td>
<td>114 (21%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>38 (7%)</td>
<td>37 (7%)</td>
<td>0.90</td>
</tr>
<tr>
<td>OAC prescription at baseline</td>
<td>264 (49%)</td>
<td>259 (48%)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence of clinical events during follow-up (/100 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE</td>
</tr>
<tr>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
</tr>
<tr>
<td>Major bleeding</td>
</tr>
<tr>
<td>All-cause death</td>
</tr>
<tr>
<td>Cardiac death</td>
</tr>
<tr>
<td>Non-cardiac death</td>
</tr>
<tr>
<td>Stroke/SE/all-cause death</td>
</tr>
</tbody>
</table>

*P value for comparison between LBW and non-LBW from log-rank test. Categorical data are presented as number (%). Abbreviations as in Tables 1,2. Vascular disease included old myocardial infarction and peripheral artery disease.

Vascular disease included old myocardial infarction and peripheral artery disease. Renal dysfunction was defined as creatinine clearance (calculated with Cockcroft-Gault formula) <60 ml/min. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.
from studies on fibrinolytic therapy and also on antiplatelet therapy for those undergoing percutaneous coronary intervention. However, the incidence of major bleeding was comparable between the LBW and non-LBW groups in the Fushimi AF Registry AF cohort. This was also the case even after adjustment by OAC prescription. As shown in Table 1, the main prescribed OAC was warfarin, and the PT-INR levels were comparable between the LBW and non-LBW groups. The reason why the incidence of major bleeding was equivalent remains elusive. The use of warfarin may be safe in LBW patients under careful monitoring of PT-INR, but longer follow-up would be needed.

Study Limitations
First, the results come from an observational study and provide only associative evidence, not causative. We cannot rule out the possibility of unmeasured or residual confounding, especially with age, even after multivariate analysis and propensity score-matching, as well as the negative P value for interaction, because advanced age and LBW were strongly associated. Although we demonstrated LBW as an independent risk factor for stroke/SE in the Fushimi AF Registry, the results need to be validated in other independent datasets. Second, among 3,304 patients, 359 patients (10.9%) were missing BW data. We believed that the missing data were unlikely to change the incidence of stroke/SE during the follow-up period. However, patients who had a higher risk profile for stroke/SE, and indeed had a higher incidence of stroke/SE during the follow-up period. However, the incidence of major bleeding was not particularly high in LBW patients under careful monitoring of PT-INR, but longer follow-up would be needed.

Conclusions
In a community-based, large prospective cohort, we demonstrated that many Japanese AF patients have LBW and they had a higher risk profile for stroke/SE, and indeed had a higher incidence of stroke/SE during the follow-up period. However, the incidence of major bleeding was not particularly high in the LBW group.

Acknowledgments
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Disclosures
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References
The following is a list of the institutions participating in the registry.


