Body Mass Index and Adverse Outcomes in Elderly Patients With Atrial Fibrillation
The AMADEUS Trial
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Background and Purpose—Obesity has been associated with increased cardiovascular risk in atrial fibrillation, but little is known in elderly patients with atrial fibrillation.

Methods—Post hoc analysis of data from the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) trial.

Results—We studied 1588 elderly patients, who were categorized as normal body mass index (BMI, 18.5–25 kg/m²; n=515 [32.4%]), overweight (BMI, 25–30 kg/m²; n=711 [44.8%]), and obese (BMI≥30 kg/m²; n=362 [22.8%]). There was a significant reduction in the composite outcome of cardiovascular death and stroke/systemic embolism with increasing BMI category, being 5.0%, 3.2%, and 1.5% per 100 patient-years, respectively (P for trend=0.01). Cox proportional hazards analysis found obesity to be associated with a lower risk of the primary composite outcome (hazard ratio, 0.29; 95% confidence interval, 0.11–0.77; P=0.01). In the warfarin arm (n=814), multivariate logistic regression analysis demonstrated that obesity was independently related to higher odds of time in therapeutic range ≥60% (odds ratio, 1.84; 95% confidence interval, 1.21–2.80; P=0.004).

Conclusion—Obesity was associated with a lower stroke and mortality rate in elderly anticoagulated atrial fibrillation patients. Obesity was related to good quality anticoagulation control. (Stroke. 2016;47:523-526. DOI: 10.1161/STROKEAHA.115.011876.)

Key Words: atrial fibrillation ■ international normalized ratio ■ mortality ■ obesity ■ stroke

Obesity is often associated with many conventional risk factors for ischemic stroke among atrial fibrillation (AF) patients and has been linked with an increased incidence of AF. Despite these data, little is known about the effect of obesity on adverse outcomes in elderly patients with AF on oral anticoagulation. When a vitamin K antagonist is used, the quality of anticoagulation control (eg, time in therapeutic range [TTR] of the international normalized ratio) is also an important determinant of thromboembolism and bleeding.

In this analysis from the AMADEUS trial (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation), we first investigated the impact of obesity on the overall rate of stroke and death in elderly patients with AF on anticoagulation in the whole trial cohort, and second, the association between obesity and TTR in warfarin arm.

Methods
The design of the AMADEUS trial has been previously described. Body mass index (BMI) was categorized with normal BMI defined as 18.5 to 25 kg/m², overweight as 25 to 30 kg/m², and obese as >30 kg/m². Underweight patients (BMI<18.5 kg/m²) were excluded from analysis because of small numbers. The primary outcome of this analysis was the composite end point of cardiovascular (CV) death and stroke/systemic embolism (SSE).

The characteristics of the patients are reported as percentages and mean (SD). Comparisons between the 3 BMI groups (18.5–25, 25–30, and ≥30 kg/m², respectively) were made using a χ² test when comparing categorical variables and the Kruskal–Wallis test for continuous variables. Outcomes by each BMI group were calculated by the overall rate of adverse events per 100 patient-years. Kaplan–Meier curve differences were assessed using a log-rank test. A Cox proportional hazard model was used to identify independent characteristics associated with outcomes, and logistic regression analysis performed to assess the relationship between BMI and good quality anticoagulation control (TTR≥60%) in warfarin arm. A 2-tailed P value<0.05 was considered statistically significant.

Results
After exclusion of patients with underweight (n=41) and age <75 years (n=2947), this analysis consisted of 1588 elderly (age ≥75 years) patients. Mean BMI was 27.2±4.5 kg/m². Significant differences between BMI groups were noted for several baseline comorbidities and outcomes (Table 1). BMI categories and primary outcomes for those aged ≥75 years are shown in Figure 1, with corresponding data for age<75 years and overall population to provide perspective. For the whole cohort, there was a significant reduction in the combined end point of CV death/SSE with

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increasing of BMI category \((P\text{ for trend}=0.01)\). In the warfarin arm only, there was a nonsignificant trend for decreasing CV death/SSE with increasing BMI category \((P\text{ for trend}=0.28)\).

A multivariate Cox proportional hazard model found that obesity was significantly associated with lower risk of the primary composite outcome in the whole cohort \((\text{hazard ratio, 0.29; 95\% confidence interval, 0.11–1.95; } P=0.06\text{ in overweight; odds ratio, 1.84; 95\% confidence interval, 1.21–2.80; } P=0.004\text{ in obese group})\). Any clinically relevant bleeding and the composite outcome of any clinically relevant bleeding, CV death, and SSE were nonsignificantly related to increasing BMI category \((P\text{ values for trend}=0.21\text{ and 0.46, respectively})\).

Kaplan–Meier curves for the primary composite outcome in the whole cohort show that overweight/obese patients were at lower risk of CV death, stroke, and SSE versus normal BMI as the reference \((\log \text{ rank test, } P=0.03; \text{Figure 2})\). Kaplan–Meier analysis for the warfarin arm shows a similar trend, but nonsignificant \((\log \text{ rank test, } P=0.54)\) because of a limitation of power.

**TTR and BMI in Warfarin Arm**

A significant trend of increasing mean TTR in the warfarin arm \((n=814)\) was seen with increasing BMI category among elderly patients, that is, 52\% in normal BMI, 57\% in overweight, and 60\% in obese group, respectively \((P\text{ for trend}<0.001)\). Multivariate logistic regression analysis demonstrated that quality of anticoagulation \((\text{TTR} \geq 60\%)\) was related to obesity \((\text{odds ratio, 1.39; 95\% confidence interval, 0.99–1.95; } P=0.06\text{ in overweight; odds ratio, 1.84; 95\% confidence interval, 1.21–2.80; } P=0.004\text{ in obese group})\). Any clinically relevant bleeding and the composite outcome of any clinically relevant bleeding, CV death, and SSE were nonsignificantly related to increasing BMI category \((P\text{ values for trend}=0.21\text{ and 0.46, respectively})\).

**Discussion**

We report the association of low BMI with more adverse outcomes among anticoagulated elderly patients with AF, and this may be related to the quality of anticoagulation control among warfarin users. This may provide one possible explanation why some patient groups with low BMI (eg, Asians) have a tendency to greater CV event rates and poorer TTR when compared with those with normal BMI.

An association between obesity and a more favorable cardiovascular prognosis (the so-called obesity paradox) has

| Table. Baseline Characteristics and Clinical Outcomes According to Body Mass Index Category |
|----------------------------------|---------------------------------|---------------------------------|---------------------|
| BMI, 18.5–25 kg/m², Normal       | BMI, 25–30 kg/m², Overweight    | BMI ≥30 kg/m², Obesity          | \(P\text{Value}\) |
| Total patients n (%)             | 515 (32.4)                      | 711 (44.8)                      | 362 (22.8)          |                        |
| Sex, men (%)                     | 281 (54.6)                      | 455 (64.0)                      | 191 (52.8)          | <0.001                 |
| Age, y (SD)                      | 79.7 (3.7)                      | 79.1 (3.3)                      | 78.6 (3.0)          | <0.001                 |
| Hypertension (%)                 | 339 (65.8)                      | 509 (71.6)                      | 281 (77.6)          | 0.001                  |
| Diabetes mellitus (%)            | 61 (11.8)                       | 111 (15.6)                      | 95 (26.2)           | <0.001                 |
| Heart failure (%)                | 114 (22.1)                      | 169 (23.8)                      | 70 (19.3)           | 0.26                   |
| Previous stroke/TIA/TE (%)       | 164 (31.8)                      | 172 (24.2)                      | 85 (23.5)           | 0.004                  |
| Coronary artery disease (%)      | 140 (27.2)                      | 252 (35.4)                      | 119 (32.9)          | 0.009                  |
| Creatinine clearance (SD)        | 49.5 (14.8)                     | 57.7 (15.9)                     | 70.6 (33.0)         | <0.001                 |
| Body mass index (SD)             | 22.8 (1.6)                      | 27.2 (1.4)                      | 33.3 (4.0)          | <0.001                 |
| CHA2DS2-VASc score (SD)          | 4.4 (1.4)                       | 4.3 (1.3)                       | 4.5 (1.5)           | 0.1                    |

Clinical outcomes, n (%/100 patient-years)

| Whole cohort                     | Combined CV death and stroke/SE | 22 (5.0)                       | 20 (3.2)            | 5 (1.5) | 0.04 (unadjusted) |
|                                 | CV death                         | 13 (2.9)                       | 12 (1.9)            | 2 (0.6) | 0.08 (unadjusted) |
|                                 | Stroke/SE                        | 10 (2.3)                       | 8 (1.3)             | 3 (0.9) | 0.30 (unadjusted) |
| Warfarin arm only                | Combined CV death and stroke/SE  | 11 (4.9)                       | 13 (3.8)            | 5 (2.7) | 0.55 (unadjusted) |
|                                 | CV death                         | 7 (3.1)                        | 6 (1.7)             | 2 (1.1) | 0.34 (unadjusted) |
|                                 | Stroke/SE                        | 5 (2.3)                        | 7 (2.1)             | 3 (1.7) | 0.92 (unadjusted) |

The combined end point of CV death and stroke/SE occurred in 47 patients (3.0\%) in whole elderly cohort. There was no significant difference by treatment arms \((18 \text{ on idraparinux vs 29 on warfarin arm, } P=0.18)\). Similarly, 12 on idraparinux and 15 on warfarin \((P=0.70)\) for the outcome of CV death; and 6 on idraparinux and 15 on warfarin \((P=0.08)\) for the outcome of stroke, respectively. CHA2DS2-VASc indicates congestive heart failure, hypertension, age ≥75 y (double), diabetes mellitus, previous stroke/transient ischemic attack/thromboembolism (double), vascular disease, age 65–74 y, and sex category (score of 1 for females; CV, cardiovascular; SE, systemic embolism; TE; thromboembolism; and TIA; transient ischemic attack.)
been reported in patients with AF, where being overweight or obese was associated with a lower risk of cardiovascular death or all-cause mortality. In contrast, an analysis from the Danish DCH cohort showed that overweight and obesity in patients with AF are risk factors for ischemic thromboembolism, or death, partly because of an unhealthy lifestyle and unmeasured comorbidity, not because of weight status per se. This study shows that among elderly patients with AF, obesity was independently associated with a better composite outcome of cardiovascular death and stroke/systemic embolism compared with the normal BMI group.

What may explain the relationship between obesity and outcomes? First, obese patients may use more cardiovascular prevention strategies more than lean or normal weight patients, given that obese patients in the elderly have more cardiovascular risk factors, such as diabetes mellitus and hypertension, which result in more contact with healthcare providers, that may also improve their TTR management. Second, obese subjects may have greater metabolic reserve than lean or normal weight patients, allowing a greater tolerance for metabolic stress. Third, obesity is associated with lower atrial natriuretic peptide levels, which can predict mortality in AF patients with heart failure.

Perhaps the much more important finding is the significant trend for improved mean TTR in warfarin arm, which is seen with an increase of BMI category. Given the close relationship between TTR and outcomes, obesity in elderly patients with AF might be linked with less adverse outcomes when compared with normal weight patients in view of their better TTR. As we are limited in power to fully explore the association between TTR and individual adverse outcomes in warfarin arm because of the low event rates, further studies are needed to explore this hypothesis.

Limitations

Although the development of idraparinux had been prematurely terminated because of a high bleeding rate, we used data from both arms in the AMADEUS trial for a meaningful analysis because long-term treatment with idraparinux was no worse than warfarin in terms of efficacy end points, for our combined outcome of CV death and stroke/SE. Also, we are testing the impact of obesity per se and not the anticoagulant regime. Of note, components of the composite outcome (stroke and mortality) in AF are both reduced by warfarin use. Although BMI is the most commonly used measurement of obesity, it does not directly distinguish between high muscle mass and high fat. Indeed, the relation of BMI to the incidence rate of primary composite outcome between elderly (age≥75) and nonelderly (age<75) groups can be explained by body fat percentage, which might be different between the two. Finally, our study does not provide evidence that advice to increase weight and becoming obese will improve the prognosis overall in anticoagulated elderly patients with AF.

In conclusion, obesity is associated with lower risk of combined CV death and stroke/systemic embolism in elderly AF patients on anticoagulation. Obesity is associated with the good quality of warfarin control (better TTRs), which may have a positive impact on adverse outcomes.

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Sanofi SA provided the study data set. The analysis of the data set was conducted fully independent of any industry or other grant support.

Disclosures

Dr Lip serves as a speaker for Bayer, BMS/Pfizer, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. Dr Lip serves as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. The other authors report no conflicts.

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