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CLINICAL RESEARCH
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Relationship between body mass index and outcomes in patients with atrial fibrillation treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial

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Aims To investigate the relationship between body mass index (BMI) and outcomes in patients with atrial fibrillation (AF).

Methods and results In the ENGAGE AF-TIMI 48 trial, patients with AF were randomized to warfarin (international normalized ratio 2.0–3.0) or edoxaban. The cohort ($N = 21\ 028$) included patients across BMI categories (kg/m^2): underweight (<18.5) in 0.8%, normal (18.5 to <25) in 21.4%, overweight (25 to <30) in 37.6%, moderately obese (30 to <35) in 24.8%, severely obese (35 to <40) in 10.0%, and very severely obese (≥40) in 5.5%. In an adjusted analysis, higher BMI (continuous, per 5 kg/m^2 increase) was significantly and independently associated with lower risks of stroke/systemic embolic event (SEE) [hazard ratio (HR) 0.88, $P = 0.0001$], ischaemic stroke/SEE (HR 0.87, $P < 0.0001$), and death (HR 0.91, $P < 0.0001$), but with increased risks of major (HR 1.06, $P = 0.025$) and major or clinically relevant non-major bleeding (HR 1.05, $P = 0.0007$). There was a significant interaction between sex and increasing BMI category, with lower risk of ischaemic stroke/SEE in males and increased risk of bleeding in women. Trough edoxaban concentration and anti-Factor Xa activity were similar across BMI groups >18.5 kg/m^2, while time in therapeutic range for warfarin improved significantly as BMI increased ($P < 0.0001$). The effects of edoxaban vs. warfarin on stroke/SEE, major bleeding, and net clinical outcome were similar across BMI groups.

Conclusion An increased BMI was independently associated with a lower risk of stroke/SEE, better survival, but increased risk of bleeding. The efficacy and safety profiles of edoxaban were similar across BMI categories ranging from 18.5 to >40.

Keywords Atrial fibrillation • Edoxaban • Obesity • Warfarin • Stroke

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with a five-fold increase in the risk of stroke, and increased mortality and hospitalizations. The incidence of AF is higher in obese patients than in non-obese patients,[1] but, in a retrospective analysis of the patients enrolled in the AFFIRM trial,[2] survival was better in obese patients with AF. In patients with AF, body mass index (BMI) is not considered to be a major risk factor for stroke or bleeding.[3] The relationship between BMI and stroke is complex and

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in the Physician's Health Study, which did not exclusively enrol patients with AF, the risks of total, ischaemic, and haemorrhagic stroke were increased with each unit increase in BMI, independently of the effects of hypertension, diabetes, and cholesterol.[4] Taking into account the effects of BMI on outcomes in the general population, it is well established that an elevated BMI is associated with higher mortality.[5,6] Furthermore, an increased risk of bleeding at lower BMI has been reported among patients with atherothrombotic disease treated with single or dual antiplatelet therapy.[7]

In the present study, we analysed the relationship between BMI and pharmacokinetic, pharmacodynamic, and clinical outcomes in patients enrolled in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial.[8,9]

Methods

The ENGAGE AF-TIMI 48 trial was a three-group, randomized, double blind, double-dummy study comparing two dose regimens of edoxaban with warfarin conducted at 1393 centres in 46 countries with a median follow-up of 2.8 years.[9] Both the study design and main results were published previously.[8,9] Briefly, the trial enrolled 21 105 patients 21 years of age or older, who had AF documented within the 12 months preceding randomization, a $CHADS_2$ score of 2 or higher, and anticoagulation therapy planned for the duration of the trial.[8] Key exclusion criteria were AF due to a reversible cause, an estimated creatinine clearance of less than 30 mL per minute, a high risk of bleeding, use of dual antiplatelet therapy, moderate-to severe mitral stenosis, other indications for anticoagulation therapy, acute coronary syndromes, coronary revascularization, or stroke within 30 days before randomization; and an inability to adhere to study procedures. There were no exclusions based on weight or BMI.[8]

Patients were randomly assigned, in a 1:1:1 ratio, to receive warfarin, dose-adjusted to achieve an international normalized ratio (INR) of 2.0–3.0, or to receive higher-dose edoxaban (HDE) or lower-dose edoxaban (LDE) regimens. The HDE group received 60 mg once daily, and the LDE group 30 mg once daily. For patients in either edoxaban group, the edoxaban dose was halved if any of the following characteristics were present at the time of randomization or during the study: estimated creatinine clearance of ≤50 mL per minute, a body weight of 60 kg or less, or the concomitant use of verapamil, quinidine, or dronedarone (P-glycoprotein inhibitors).[8] Since only the HDE regimen has been approved for clinical use, we present the data with the LDE regimen in the Supplementary material online, *Appendix*.

Baseline characteristics were presented as medians (interquartile ranges) for continuous variables and frequencies for categorical variables. Creatinine clearance was estimated by the Cockroft–Gault equation using the actual body weight,[10] similarly to the other trials on non-vitamin K antagonist oral anticoagulants.[11] Body mass index was calculated in kg/m^2 from the height and weight obtained at baseline and used to classify patients into six categories, per the International Obesity Task Force and the World Health Organization: underweight: <18.5; normal: 18.5 to <25; overweight: 25 to <30; moderately obese: 30 to <35; severely obese: 35 to <40; and very severely obese: ≥40.[12] Baseline characteristics were compared across these six BMI categories with a linear trend test using a generalized linear model for continuous variables and Cochran–Armitage trend test for categorical variables.

Trough blood samples were collected 1 month after randomization and plasma concentrations of edoxaban and anti-Factor Xa activity were measured as previously described.[13] Trough values were compared across the categorical groups of BMI, stratified by dose reduction status, to permit comparison of patients who received similar doses of edoxaban.

In the primary analyses of clinical outcomes, the relationships between continuous BMI and outcomes were estimated using a Cox proportional hazard model to derive predicted unadjusted and adjusted hazard ratios (HR) while accounting for the time to event.[14] The proportional hazards assumption was confirmed with Schoenfeld residuals and by plotting the log negative-log of the survival function by log of time. Kaplan–Meier curves were used to calculate survival rates.

In the secondary analyses, HRs with 95% confidence intervals (CIs) were estimated using adjusted Cox proportional hazard models to explore the relationships between the BMI categories and clinical outcomes. Covariates in the multivariable models included the three-level randomized treatment (warfarin, HDE, and LDE), $CHADS_2$ score at screening, verapamil, or quinidine use at screening, paroxysmal vs. non-paroxysmal AF, sex, region, age (as a continuous variable), previous use of vitamin K antagonist for ≥60 days, baseline use of aspirin, thienopyridine agents, amiodarone, digoxin or digitalis preparations, smoking status, history of hypertension, stroke or transient ischaemic attack (TIA), heart failure, diabetes, and creatinine levels at baseline. The group of patients with normal BMI (from 18.5 to <25 kg/m^2) was used as the referent. Interactions between the randomized treatment and BMI categories were tested by Cox proportional hazard modelling to address effect modification by BMI group.

In view of the small sample size ($n = 177$), data in patients with BMI <18.5 kg/m^2 were presented separately in the Supplementary material online, *Appendix*. Event rates were expressed per 100 patient-years. Clinical outcomes were as defined in the ENGAGE AF-TIMI 48 trial.[9] The primary efficacy endpoint was the composite of adjudicated stroke or systemic embolic events (SEE) in the intention-to-treat population counting all events whether on or off study drug. The principal safety endpoint was adjudicated ISTH major bleeding in the safety population while on treatment. Additional endpoints included ischaemic stroke/SEE, mortality, major or clinically relevant non-major bleeding, and a net clinical outcome (composite of stroke, systemic embolic event, major bleeding, or death). An independent clinical endpoint committee, whose members were unaware of the study assignment, adjudicated all clinical events.

All statistical tests were two-sided with a *P*-value <0.05 considered to be significant, without adjustment for multiplicity. Analyses were performed with use of Stata/SE version 12.1 (Stata Corp., College Station, TX, USA).

Results

Data on BMI were available in 21 028 of the 21 105 patients enrolled (99.6%). The distribution of the patient population into BMI categories is shown in *Figure 1*: underweight (<18.5) in 177 (0.8%), normal (18.5 to <25) in 4491 (21.4%), overweight (25 to <30) in 7903 (37.6%), moderately obese (30 to <35) in 5209 (24.8%), severely obese (35 to <40) in 2099 (10.0%), and very severely obese (≥40) in 1149 (5.5%). A BMI >50 kg/m^2 was present in only 0.7% of the cohort (148 patients). As shown in *Table 1*, the distribution of BMI varied across regions, with obesity most common in North America and Eastern Europe, while almost two-thirds of patients who were underweight were enrolled in Asia. As expected, a history of diabetes was common among patients who were overweight or obese. Creatinine clearance was

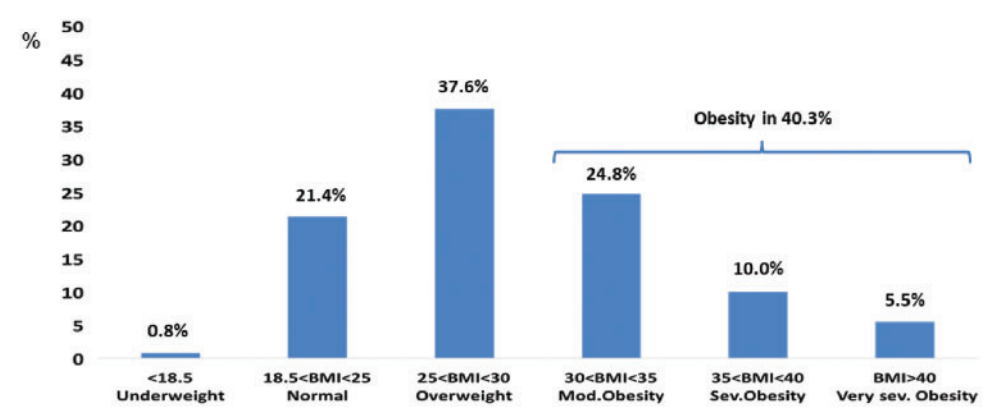


Figure 1 Distribution of body mass index (kg/m^2) in the ENGAGE AF-TIMI 48 population. Groups are shown according to body weight in kg/m^2. BMI, body mass index; Mod., Moderate; Sev., Severe.

directly correlated with BMI (Pearson $r = 0.57$, $P < 0.0001$). The proportions of patients at randomization treated with renin-angiotensin system/aldosterone receptor inhibitors, lipid lowering agents, and beta-blockers were significantly greater in patients in the higher BMI categories (*Table 1*). Age ≥75 years, impaired renal function, previous TIA/stroke, and lack of prior VKA experience were more common among patients with lower values of BMI. Data on high-sensitivity C-reactive protein (hs-CRP) were available in 4680 patients; no differences were found across BMI categories (*Table 1*).

Patients randomized to warfarin, HDE, and LDE were similar within each BMI group (Supplementary material online, *Table S1A–C* in *Appendix*).

Pharmacokinetic and pharmacodynamic data

In patients randomized to warfarin, the median time in therapeutic range (TTR) increased as BMI increased (*P* trend <0.0001, Supplementary material online, *Figure S1*). This finding was driven by a lower median TTR in underweight patients (59%), whereas the median TTRs were fairly similar (67–69%) for patients with BMI ≥18.5 kg/m^2, with slightly higher TTRs as BMI increased. The proportion of time with a subtherapeutic INR (i.e. <2) was significantly lower at increasing BMIs (*P* trend= 0.0007, Supplementary material online, *Table S2*). The proportion of time with an INR >3 was similar across BMI groups above 18.5 kg/m^2 at 12.1–12.5% (*P* trend = 0.58, Supplementary material online, *Table S2*).

Trough edoxaban plasma concentrations measured at 1 month after randomization in the HDE group did not differ across BMI categories (*Table 2*), either among patients who were dose reduced at randomization (*P* trend = 0.17) or in patients who were not dose reduced at randomization (*P* trend = 0.28). Likewise, there were no differences across BMI categories in anti-Factor Xa activity at trough in patients who were (*P* trend = 0.77) or were not dose reduced at randomization (*P* trend = 0.73) (*Table 2*).

Body mass index as a continuous variable and clinical outcomes

Figure 2 shows the adjusted HRs for BMI as a continuous variable (in units of 5 kg/m^2 increase) and clinical outcomes in the whole cohort. Higher BMI was significantly and independently associated with lower risks of stroke/SEE (HR 0.88, 95% CI 0.82–0.94, $P = 0.0001$), ischaemic stroke/SEE (HR 0.87, 95% CI 0.81–0.93, $P < 0.0001$), and of death (HR 0.91, 95% CI 0.87–0.95, $P = 0.0001$). However, increasing BMI was independently associated with a greater risk of major bleeding (HR 1.06, 95% CI 1.01–1.12, $P = 0.025$) and of major or clinically relevant non-major bleeding (HR 1.05, 95% CI 1.02–1.08, $P = 0.0007$).

In the Supplementary material online, *Appendix*, cubic splines curves show the relationship between BMI and different clinical outcomes, both unadjusted (Supplementary material online, *Figure S2*) and adjusted (Supplementary material online, *Figure S3*).

Categories of body mass index and outcomes

In an adjusted analysis considering the specific BMI categories with BMI ≥18.5 kg/m^2 (i.e. excluding underweight patients), the risks of stroke/SEE, ischaemic stroke/SEE, and death were significantly lower as BMI increased (especially at BMIs ≥35 kg/m^2) (*Table 3*). Conversely, at higher BMI categories there were significantly increased risks of major bleeding and of major or clinically relevant non-major bleeding, consistent with the results of the analysis of BMI as a continuous variable. In contrast, there was no relationship between BMI and the net outcome (*P* trend = 0.44 across increasing BMI categories). These results were generally consistent across the geographical regions, despite large regional differences in the distributions of BMI.

There was a significant interaction between sex and BMI in the whole cohort (adjusted analysis) with regard to ischaemic stroke/SEE ($P = 0.032$) and major or clinically relevant non-major bleeding ($P < 0.01$). As shown in Supplementary material online, *Table S3*, in male patients a significantly lower risk of ischaemic stroke/SEE was found across increasing BMI categories ($P < 0.005$) but this was not seen in women. In women, a significantly increased risk of major or

Table 1 Baseline characteristics of all patients stratified by categories of body mass index

Body mass index (kg/m^2)	Underweight (<18.5)	Normal (18.5 to <25)	Overweight (25 to <30)	Moderately obese (30 to <35)	Severely obese (35 to <40)	Very severely obese (≥40[a])	*P*-value for trend	Standardized test statistic value[b]
N (%)	177 (0.8)	4491 (21.4)	7903 (37.6)	5209 (24.8)	2099 (10.0)	1149 (5.5)	NA	
Median (IQR) of BMI	17.6 (16.7–18.1)	23.2 (21.9–24.2)	27.5 (26.3–28.7)	32.0 (30.9–33.3)	36.8 (35.8–38.1)	43.4 (41.3–46.5)	<0.0001	
Age (years)								
Median	75	75	73	71	68	64	<0.0001[c]	
25–75 percentile	68–82	70–81	67–79	65–78	61–75	58–70		
Female sex	102 (57.6)	1784 (39.7)	2667 (33.7)	1947 (37.4)	944 (45.0)	556 (48.4)	<0.0001	-5.97
Region								
North America	18 (10.2)	739 (16.5)	1543 (19.5)	1206 (23.2)	619 (29.5)	539 (46.9)	<0.0001	-22.49
Latin America	22 (12.4)	605 (13.5)	1046 (13.2)	662 (12.7)	240 (11.4)	79 (6.9)	<0.0001	5.24
Western Europe	10 (5.6)	598 (13.3)	1288 (16.3)	840 (16.1)	322 (15.3)	135 (11.7)	0.34	-0.95
Eastern Europe	11 (6.2)	1030 (22.9)	2778 (35.2)	2149 (41.3)	829 (39.5)	345 (30.0)	<0.0001	-13.98
Asia–Pacific, South Africa	116 (65.5)	1519 (33.8)	1248 (15.8)	352 (6.8)	89 (4.2)	51 (4.4)	<0.0001	39.69
Paroxysmal AF	48 (27.1)	1191 (26.5)	1983 (25.1)	1345 (25.8)	500 (23.8)	281 (24.5)	0.054	1.93
Qualifying risk								
Age ≥75 years	91 (51.4)	2301 (51.2)	3575 (45.2)	1766 (33.9)	549 (26.2)	148 (12.9)	<0.0001	30.14
Prior stroke or TIA	78 (44.1)	1670 (37.2)	2332 (29.5)	1252 (24.0)	425 (20.2)	199 (17.3)	<0.0001	19.17
Congestive heart failure	103 (58.2)	2374 (52.9)	4415 (55.9)	3135 (60.2)	1319 (62.8)	738 (64.2)	<0.0001	-10.07
Diabetes mellitus	20 (11.3)	1041 (23.2)	2526 (32.0)	2193 (42.1)	1092 (52.0)	725 (63.1)	<0.0001	-33.22
Hypertension	127 (71.8)	3913 (87.1)	7404 (93.7)	5066 (97.3)	2056 (98.0)	1118 (97.3)	<0.0001	-21.97
$CHADS_2$ score	2.8 ± 0.9	2.9 ± 1.0	2.9 ± 1.0	2.8 ± 1.0	2.8 ± 0.9	2.7 ± 0.9	0.059	3.56
≤3	140 (79.1)	3371 (75.1)	6022 (76.2)	4089 (78.5)	1678 (79.9)	973 (84.7)	<0.0001	-7.62
4–6	37 (20.9)	1120 (24.9)	1881 (23.8)	1120 (21.5)	421 (20.1)	176 (15.3)	<0.0001	7.62
Dose reduced at randomization	175 (98.9)	2507 (55.8)	1788 (22.6)	636 (12.2)	177 (8.4)	48 (4.2)	<0.0001	53.41
CrCl ≤50 (mL/min)	117 (66.1)	1779 (39.6)	1539 (19.5)	493 (9.5)	108 (5.1)	20 (1.7)	<0.0001	43.76
Weight ≤60 kg	175 (98.9)	1648 (36.7)	241 (3.0)	7 (0.1)	1 (0.0)	0 (0.0)	<0.0001	57.7
Verapamil or quinidine	10 (5.6)	197 (4.4)	271 (3.4)	162 (3.1)	86 (4.1)	30 (2.6)	0.007	2.69
CrCl (mL/min)								
Median	44.4	54.1	66.7	81.5	94.9	117.6	<0.0001[c]	
25–75 percentile range	35.3–53.6	42.7–65.6	52.2–81.3	63.0–100.1	72.3–117.5	88.9–146.4		
VKA experienced	67 (37.9)	2481 (55.2)	4661 (59.0)	3109 (59.7)	1311 (62.5)	765 (66.6)	<0.0001	-8.69
Medication at randomization								
Aspirin	66 (37.3)	1298 (28.9)	2271 (28.7)	1553 (29.8)	600 (28.6)	381 (33.2)	0.11	-1.6
Thienopyridine	10 (5.6)	130 (2.9)	197 (2.5)	87 (1.7)	41 (2.0)	20 (1.7)	<0.0001	4.36
Amiodarone	17 (9.6)	492 (11.0)	928 (11.7)	680 (13.1)	240 (11.4)	123 (10.7)	0.26	-1. 12
Digoxin or digitalis	78 (44.1)	1609 (35.8)	2242 (28.4)	1445 (27.7)	609 (29.0)	326 (28.4)	<0.0001	7.12

Continued

Table 1 Continued

Body mass index (kg/m^2)	Underweight (<18.5)	Normal (18.5 to <25)	Overweight (25 to <30)	Moderately obese (30 to <35)	Severely obese (35 to <40)	Very severely obese (≥40[a])	*P*-value for trend	Standardized test statistic value[b]
Renin-angiotensin system/aldosterone receptor inhibitors	74 (41.8)	2641 (58.8)	5226 (66.1)	3660 (70.3)	1508 (71.8)	770 (67)	<0.0001	-11.9
Lipid lowering agents	41 (23.2)	1726 (38.4)	3806 (48.2)	2706 (51.9)	1120 (53.4)	642 (55.9)	<0.0001	-15.36
Beta-blockers	79 (44.6)	2554 (56.9)	5281 (66.8)	3679 (70.6)	1494 (71.2)	850 (74)	<0.0001	-15.67
Smoking								
Current smoker	14 (7.9)	371 (8.3)	590 (7.5)	353 (6.8)	148 (7.1)	71 (6.2)	0.003	2.99
Former smoker	48 (27.1)	1399 (31.2)	2690 (34.0)	1794 (34.5)	731 (34.8)	416 (36.2)	<0.0001	-4.1
Never smoker	115 (65.0)	2720 (60.6)	4622 (58.5)	3060 (58.8)	1220 (58.1)	662 (57.6)	0.019	2.36
N patients with hs-CRP	11	815	1865	1336	539	287		
Baseline hs-CRP (mg/L)	2.5 ± 4.32	5.2 ± 9.13	5.6 ± 12.19	5.3 ± 10.4	5.6 ± 13.02	5.5 ± 10.7	0.36	0.84

Data shown are *n* (%) unless otherwise indicated.
AF, atrial fibrillation; CrCl, creatinine clearance; TIA, transient ischaemic attack.
[a]There were 148 patients with BMI >50.
[b]F-value for continuous variables and Z-value for categorical variables.
[c]*P* for trend with Jonckheere–Terpstra test.

clinically relevant non-major bleeding ($P < 0.0001$) was found across increasing BMI categories; however, the same was not present in men.

The increased risk of major bleeding across increasing BMI categories was even more evident in an analysis adjusted by hs-CRP, (Supplementary material online, *Table S4*).

Efficacy and safety of higher-dose edoxaban vs. warfarin according to body mass index

There was no significant interaction between BMI analysed as a categorical variable and the outcomes of stroke/SEE, all-cause mortality, major bleeding, major or clinically relevant non-major bleeding, or the net clinical outcome (*P* for interaction ≥0.16 for each outcome, Supplementary material online, *Table S5*). In contrast, the *P* for interaction was 0.047 for the endpoint of ischaemic stroke/SEE, suggesting less protection with HDE relative to warfarin at BMIs ≥ 35. This *P* value should be cautiously interpreted due to the low number of events ($N = 10$) in the very severely obese group.

Results with lower-dose edoxaban

Trough edoxaban concentration and anti-Factor Xa activity in patients randomized to LDE, were approximately half that observed with HDE, and did not show significant variation across BMI groups (Supplementary material online, *Table S6A and B*). The risk of ischaemic stroke/SEE among patients with normal BMI and in patients with BMI ≥ 35 kg/m^2 were significantly higher in patients treated with LDE vs. warfarin (Supplementary material online, *Table S7*). Bleeding events were significantly reduced with LDE compared to warfarin across BMI groups, with no interactions between BMI and bleeding.

Exploratory analysis of underweight patients

An analysis of 177 underweight patients (BMI <18.5 kg/m^2) showed significantly increased adjusted risks, as compared to patients with a normal BMI, for multiple adverse outcomes, including all-cause mortality; the composite of stroke, systemic embolic event, or death from cardiovascular causes (including bleeding); as well as the composite of stroke, systemic embolic event, major bleeding, or death (Supplementary material online, *Figure S4*). Comparisons by randomized treatment were not performed given the small number of underweight patients enrolled.

Discussion

The present analysis of clinical outcomes in patients with AF treated with either edoxaban or warfarin from the ENGAGE AF-TIMI 48 trial with regard to BMI demonstrated the following major findings (*Take home figure*):

(1) Obesity was present in more than 40% of the enrolled population. There were pronounced regional variations, with obesity most common in North America and Eastern Europe.
(2) Higher BMI was independently associated with lower adjusted risks of stroke/SEE and of death. Higher BMI was associated with an

Table 2 Concentration and anti-Factor Xa activity at trough with the higher-dose edoxaban regimen according to body mass index categories in the sample of patients who fulfilled (top) and not fulfilled (bottom)[a] the criteria for edoxaban dose reduction

Body mass index (kg/m^2)		Underweight (<18.5)	Normal (18.5 to <25)	Overweight (25 to <30)	Moderately obese (30 to <35)	Severely/very severely obese (≥35)	*P*-value for trend
Patients with edoxaban dose reduction at randomization							
Trough edoxaban concentration	*N* patients	25	369	268	119	39	
(ng/mL)	Median	27.0	25.3	29.9	28.4	27.5	0.17
	25–75 percentile	23.4–61.1	14.0–42.4	14.7–48.1	14.4–44.6	18.0–50.2	
Trough anti-Factor Xa activity	*N* patients	15	136	108	46	19	
(IU/mL)	Median	0.45	0.47	0.53	0.60	0.54	0.77
	25–75 percentile	0.11–1.30	0.29–0.81	0.30–0.87	0.30–0.85	0.31–0.82	
Patients without edoxaban dose reduction at randomization							
Trough edoxaban concentration	*N* patients	1[a]	304	950	761	479	
(ng/mL)	Median	N/A	34.9	37.6	36.2	33.0	0.28
	25–75 percentile	N/A	19.9–60.4	20.4–62.0	19.3–61.9	16.7–62.7	
Trough anti-Factor Xa activity	*N* patients	0	97	433	358	238	
(IU/mL)	Median	N/A	0.78	0.62	0.66	0.64	0.73
	25–75 percentile	N/A	0.42–1.17	0.37–1.06	0.36–1.15	0.37–1.16	

[a]Only one patient with BMI <18.5 was not dose-reduced and data are not shown.

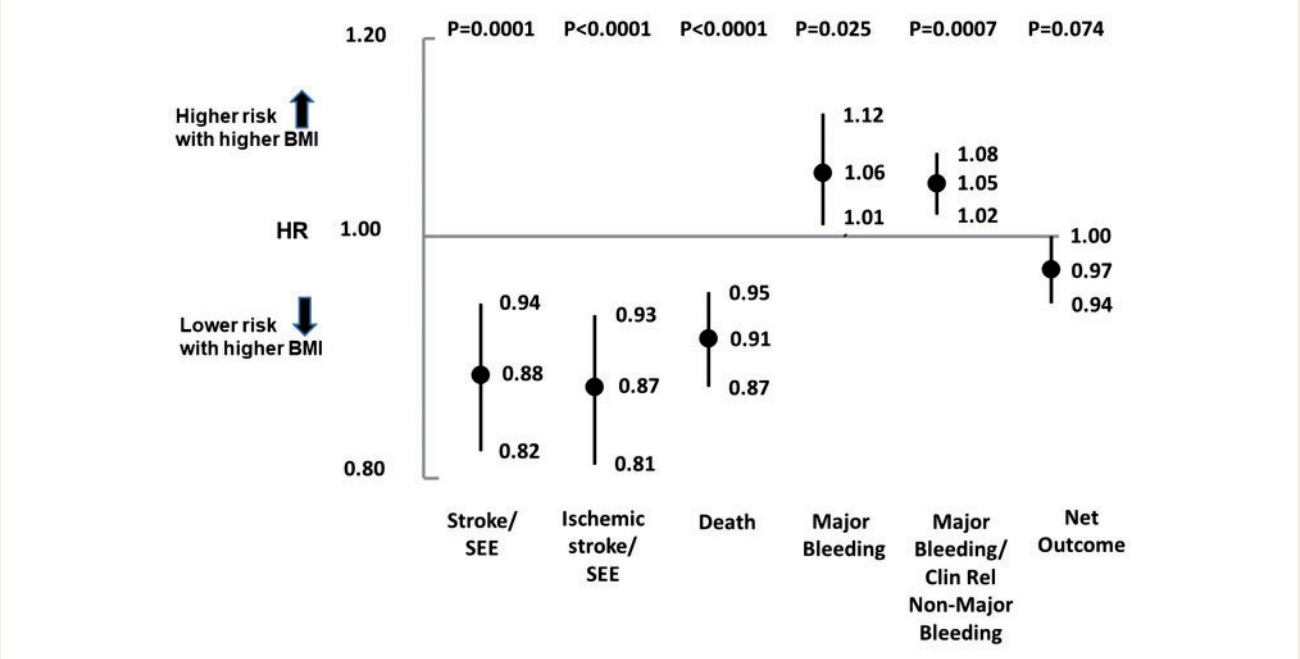


Figure 2 Results of a multivariable model with body mass index as a continuous variable per units of 5 kg/m^2 increase in body mass index. Adjusted hazard ratios (95% confidence interval) and *P*-values are shown. The graph is in logarithmic scale. The model is adjusted for treatment group, $CHADS_2$ score at screening, verapamil or quinidine use at screening, paroxysmal vs. non-paroxysmal atrial fibrillation, sex, region, age, previous use of vitamin K antagonist for ≥60 days, baseline use of aspirin, thienopyridine agents, amiodarone, digoxin or digitalis preparations, smoking status, history of hypertension, stroke or transient ischaemic attack, congestive heart failure, diabetes, and creatinine at baseline. Clin Rel non-major bleeding, clinically relevant non-major bleeding; HR, hazard ratio; S/SEE, stroke or systemic embolic event.

Table 3 Outcomes from a multivariable model according to body mass index categories (adjusted analysis)

Body mass index (kg/m^2)	Normal (18.5 to <25) *N.* of events (%)	Overweight (25 to <30) HR[a] (95% CI)	Moderately obese (30 to <35) HR[a] (95% CI)	Severely obese (35 to <40) HR[a] (95% CI)	Very severely obese (≥40) HR[a] (95% CI)	*P* for trend
Stroke/SEE	273 (2.3)	0.91 (0.78–1.07)	0.82 (0.68–1.00)	0.68 (0.52–0.89)	0.54 (0.35–0.83)	<0.001
Ischaemic Stroke/SEE	229 (2.0)	0.91 (0.77–1.09)	0.80 (0.65–0.98)	0.70 (0.52–0.94)	0.48 (0.30–0.77)	<0.001
Mortality	629 (5.2)	0.79 (0.71–0.87)	0.77 (0.68–0.88)	0.75 (0.63–0.9)	0.78 (0.62–0.98)	0.037
Major bleeding	283 (2.9)	1.03 (0.88–1.20)	1.12 (0.94–1.34)	1.18 (0.94–1.48)	1.28 (0.96–1.70)	0.045
Net outcome[b]	987 (8.7)	0.91 (0.83–0.98)	0.92 (0.83–1.01)	0.87 (0.77–1.00)	0.95 (0.80–1.12)	0.44
Major or clinically relevant non-major bleeding	1014 (11.8)	1.05 (0.97–1.14)	1.10 (1.00–1.20)	1.17 (1.04–1.32)	1.27 (1.10–1.47)	<0.001
Any bleeding	1234 (15.0%)	1.04 (0.97–1.12)	1.06 (0.97–1.15)	1.15 (1.04–1.28)	1.23 (1.08–1.40)	<0.001

BMI, body mass index; CI, confidence interval; HR, hazard ratio; SEE, systemic embolic event.
[a]Adjusted hazard ratio with normal BMI as the referent. The model is adjusted for treatment group, $CHADS_2$ score at screening, verapamil or quinidine use at screening, paroxysmal vs. non-paroxysmal AF, sex, region, age, previous use of vitamin K antagonist for ≥60 days, baseline use of aspirin, thienopyridine agents, amiodarone, digoxin or digitalis preparations, smoking status, history of hypertension, stroke or TIA, CHF, diabetes, and creatinine at baseline.
[b]Net outcome: composite of stroke, systemic embolic event, major bleeding, or death.

increased risk of bleeding, despite good control of INR in the warfarin group and no difference in edoxaban concentrations or anti-Factor Xa activity, as the BMI increased. The net clinical outcome did not differ in higher as compared to normal BMI categories. The relationship between BMI and outcomes varied by sex. In men, as BMI increased, the risk of stroke/SEE declined, but this was not the case in women. In women, as BMI increased, there was a significantly increased risk of bleeding, but this same trend was not present in men.

(3) The efficacy and safety profiles of edoxaban relative to well-managed warfarin were similar across BMI groups. The similar pharmacokinetic and pharmacodynamic results with edoxaban across the range of BMIs support the clinical observations.

The associations between BMI and outcomes in patients with AF have been the subject of growing interest in recent years, with investigations based on observational studies, from *post hoc* analyses of randomized controlled trials comparing warfarin with non-vitamin K antagonist oral anticoagulants (NOACs) and meta-analyses.[2,14–19]

Separate analyses from two NOACs trials (ARISTOTLE[15] and ROCKET-AF[16]), each showed that an increased BMI was associated with better outcomes. In the ROCKET-AF trial, an increased BMI was associated with a lower risk of stroke and systemic embolism. In an adjusted analysis of the ARISTOTLE trial, an increased BMI was associated with a lower risk of all-cause mortality, as well as lower risks of the composite of stroke, systemic embolism, myocardial infarction, or all-cause mortality. In both studies no differences in the relative effects of NOACs (rivaroxaban and apixaban, respectively) vs. warfarin on stroke/systemic embolism were found in comparisons across the different categories of BMI.

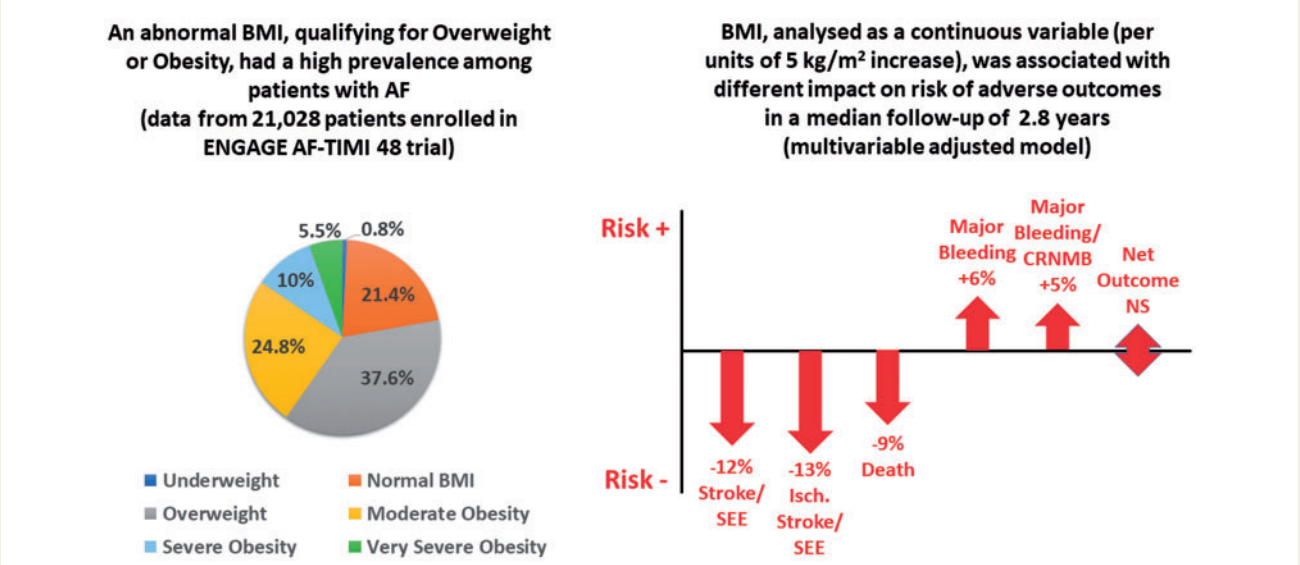
With respect to bleeding, an increased risk of incident intracerebral haemorrhage was previously reported in obese patients with no previous vascular disease.[5,20,21] Moreover, in another cohort study an increased risk of major bleeding was found in obese patients treated with warfarin and followed for 1 year.[22] However, these findings were not replicated in either the ARISTOTLE[15] or ROCKET-AF trials.[16] More recently, a meta-analysis of trials on NOACs[19] that included data from RCTs with apixaban, dabigatran, or rivaroxaban (but not ENGAGE AF-TIMI 48) found no increase in major bleeding in obese patients, as compared to normal or overweight patients.

Our analyses differed from the prior findings[15,16] since BMI was analysed with greater granularity, both as a categorical (consistent with the WHO criteria[12]), which distinguish different degrees of obesity), as well as a continuous variable. We extended prior findings by assessing the impact of BMI and treatment on a series of outcomes, including a variety of cardiovascular events and different degrees of bleeding severity over a median of 2.8-year follow-up. Moreover, we evaluated pharmacokinetic (edoxaban concentration) and pharmacodynamic measures (anti-Factor Xa activity, INR) according to BMI, thus providing data that have not been presented in prior analyses.

Our findings regarding an increase in bleeding at higher BMIs are noteworthy because they occurred despite similar edoxaban concentrations and anti-Factor Xa activity and similar TTRs (in the warfarin patients) across the range of BMIs studied. The mechanism for the increased risk in bleeding at higher BMIs is unclear. Moreover, the increased risk of bleeding at higher BMI was confirmed also in the analysis adjusted by hs-CRP levels at baseline. The latter analysis was performed since higher BMIs are associated with higher hs-CRP concentrations (an expression of low-grade systemic inflammation[23]), and hs-CRP has been evaluated as a marker of an increased risk of vascular events, including ischaemic and haemorrhagic stroke.[24]

The finding that the increased risk of bleeding at increasing BMI is more pronounced in women has practical implications in terms of the need for more aggressive management of bleeding risk factors in women.

Since obesity may change the pharmacokinetics of several drugs, the use of dosing algorithms that do not account for high BMIs has raised the question of the ideal dose of NOACs in obese patients.[20,25] Our pharmacokinetic and pharmacodynamic findings with edoxaban that demonstrate consistent results in patients with normal and high BMI support the clinical data showing preservation



Take home figure An abnormal body mass index, qualifying for overweight or obesity, had a high prevalence among patients with atrial fibrillation and was associated with different impact on risk of adverse outcomes (analysis of body mass index as a continuous variable, per units of 5 kg/m^2 increase, in a multivariable model adjusted for treatment group, $CHADS_2$ score at screening, verapamil or quinidine use at screening, paroxysmal vs. non-paroxysmal atrial fibrillation, sex, region, age, previous use of vitamin K antagonist for ≥60 days, baseline use of aspirin, thienopyridine agents, amiodarone, digoxin or digitalis preparations, smoking status, history of hypertension, stroke or transient ischaemic attack, CHF, diabetes, and creatinine at baseline). CRNMB, clinically relevant non-major bleeding; Isch. stroke, ischaemic stroke; NS, not significant; SEE, systemic embolic event.

of the efficacy and safety profile of HDE as compared to warfarin across the range of BMIs studied. This information can be useful in clinical practice for the selection of the optimal anticoagulant for obese patients. More data are needed in patients with extremely high BMI (>50 kg/m^2), particularly considering the increasing prevalence of morbid obesity.[26]

The decline in the adjusted risks of stroke/SEE and death observed at increasing BMI in ENGAGE AF-TIMI 48 is compatible with the intriguing concept of an 'obesity paradox'.[2] According to this controversial concept, although obesity is an important cardiovascular risk factor in the general population,[5,6] patients with established cardiovascular disease and an elevated BMI experience better outcomes than patients with a normal BMI.[2,15] Such findings have been reported in several cardiovascular disease states including stable coronary artery disease, acute coronary syndromes, heart failure with reduced ejection fraction and AF.[2,15–19,27] The reason(s) for an apparent protective effect of obesity are unclear and the subject of debate.[27] One hypothesis that has been proposed to explain this paradox is that by virtue of being obese, patients are offered earlier and more aggressive treatments to manage cardiovascular risk factors.[2] This may be related to the earlier, more intensive and closely monitored use of anti-hypertensive and anti-dyslipidaemic medications. Data from the Physician's Health Study[4] showed that when obese patients are not aggressively managed then the risks of total, ischaemic, and haemorrhagic stroke actually rises at increasing BMI. In our cohort, an increased use at randomization of renin-angiotensin system/aldosterone receptor inhibitors, lipid lowering agents and beta-blockers in patients in the higher BMI categories was observed. Since patients cannot be randomized to different levels of BMI, the presence of bias and confounding represent serious challenges to establishing a causal relationship in any interpretation of the 'obesity paradox'.[28,29] Moreover, according to recent population-based data,[31] the obesity paradox should be approached with great caution since it may be related to an earlier diagnosis of cardiovascular disease and a greater proportion of life lived with cardiovascular morbidity. In this context, population studies taking a life course perspective may lead to different and more reliable findings as compared to studies evaluating the follow-up of inception cohorts of patients collected at the time of diagnosis of a cardiovascular disease.[30]

The relationship between adiposity and outcomes is complicated further by pathophysiological studies that analysed adipose tissue deposits and identified metabolically healthy and unhealthy obese phenotypes on the basis of absence/presence of insulin resistance, metabolic syndrome, level of cardio-respiratory fitness, amount of visceral fat, and level of systemic inflammatory mediators.[27] A more detailed and nuanced approach to evaluate the impact of obesity on outcomes should analyse the real prevalence of the metabolically healthy obese phenotype in specific populations, including AF patients, and provide clues for clinical identification of these two distinct phenotypes.[27] Moreover, recent studies evaluated body fat distribution and highlighted the role that epicardial fat may have in the pathophysiology of AF (as well as of heart failure and coronary atherosclerosis), involving a complex interplay of inflammation, fibrosis, and vascularization.[31,32]

While awaiting further evidence, we believe that the controversies regarding the obesity paradox should not reduce the efforts of physicians in encouraging the adoption of appropriate strategies for weight-loss, increasing physical activity and exercise, in view of the

general unhealthy implications of obesity and in accordance with consensus guidelines.[24,33–35] Appropriate patient education and patient empowerment are specifically recommended by the Guidelines on AF management written by the European Society of Cardiology in collaboration with European Association for Cardio-Thoracic Surgery in 2016.[35] In obese patients, weight loss together with management of other risk factors constitute essential goals for reducing AF burden and symptoms, and for improving outcomes.

Finally, additional data are needed since the obesity paradox may simply reflect a lack of understanding of the complex pathophysiology of obesity and of the association between adiposity and cardiovascular diseases, including AF.

Strengths and limitations

The strengths of our study include the analysis of data from the largest and longest trial of a NOAC in patients with AF, with the availability of pharmacokinetic and pharmacodynamic data to support the clinical observations. The limitations include the use of a clinical trial population with relatively few patients with extreme BMIs (<18.5 kg/m^2 or >50 kg/m^2), which limit the generalizability of these results. Despite adjustment for multiple variables, we cannot exclude the possibility of residual confounding due to unmeasured covariates. Lastly, trough edoxaban concentration and anti-Factor Xa activity were analysed at 1 month after randomization and were not available immediately prior to an event.

Conclusions

In the ENGAGE AF-TIMI 48 trial consisting of patients with atrial fibrillation treated with an oral anticoagulant, clinical event rates differed across the spectrum of BMI. An increased BMI was independently associated with a lower risk of stroke/SEE, better survival, but an increased risk of bleeding. Sex modified the influences of BMI on outcomes: in men, an increased BMI was associated with a reduced risk of stroke/SEE, while in women there was an increased risk of bleeding at higher BMIs. The concentrations of edoxaban and anti-Factor Xa activity, the TTR in the warfarin group, and the relative efficacy and safety of HDE compared with warfarin did not vary significantly according to BMI. Given the findings of the present study, clinicians should consider that obese patients with AF may have lower risk of stroke but higher risk of bleeding, as compared to patients with normal BMI. Therefore, we believe that NOACs with a better balance of safety and efficacy than warfarin should be prioritized in obese patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Wang TJ, Parise H, Levy D, D'Agostino RB, Wolf PA, Vasan RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;**292**:2471–2477.
2. Badheka AO, Rathod A, Kizilbash MA, Garg N, Mohamad T, Afonso L, Jacob S. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. *Am J Med* 2010;**123**:646–651.
3. Lip GY, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. *JAMA* 2015;**313**:1950–1962.
4. Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR, Buring JE, Manson JE. Body mass index and the risk of stroke in men. *Arch Intern Med* 2002;**162**:2557–2562.
5. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;**373**:1083–1096.
6. Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, Ben-Ami Shor D, Tzur D, Afek A, Shamiss A, Haklai Z, Kark JD. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. *N Engl J Med* 2016;**374**:2430–2440.
7. Mak KH, Bhatt DL, Shao M, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Montalescot G, Steg PG, Steinhubl SR, Fox KA, Topol EJ. The influence of body mass index on mortality and bleeding among patients with or at high-risk of atherothrombotic disease. *Eur Heart J* 2009;**30**:857–865.
8. Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, Hanyok J, Patel I, Shi M, Salazar D, McCabe CH, Braunwald E. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* 2010;**160**:635–641.
9. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.
10. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.
11. Boriani G, Savelieva I, Dan GA, Deharo JC, Ferro C, Israel CW, Lane DA, La Manna G, Morton J, Mitjans AM, Vos MA, Turakhia MP, Lip GY. Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society. *Europace* 2015;**17**:1169–1196.
12. WHO Consultation on Obesity. Geneva: World Health Organization; 2000. www.who.int/iris/handle/10665/42330 (3 December 2017).
13. Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF, Deenadayalu N, Jarolim P, Betcher J, Shi M, Brown K, Patel I, Mercuri M, Antman EM. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomized, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* 2015;**385**:2288–2295.
14. Govindarajulu US, Spiegelman D, Thurston SW, Ganguli B, Eisen EA. Comparing smoothing techniques in Cox models for exposure-response relationships. *Stat Med* 2007;**26**:3735–3752.
15. Sandhu RK, Ezekowitz J, Andersson U, Alexander JH, Granger CB, Halvorsen S, Hanna M, Hijazi Z, Jansky P, Lopes RD, Wallentin L. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. *Eur Heart J* 2016;**37**:2869–2878.
16. Balla SR, Cyr DD, Lokhnygina Y, Becker RC, Berkowitz SD, Breithardt G, Fox KAA, Hacke W, Halperin JL, Hankey GJ, Mahaffey KW, Nessel CC, Piccini JP, Singer DE, Patel MR. Relation of risk of stroke in patients with atrial fibrillation

to body mass index (from patients treated with rivaroxaban and warfarin in the rivaroxaban once daily oral direct factor Xa inhibition compared with Vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation trial). *Am J Cardiol* 2017;**119**:1989–1996.
17. Senoo K, Lip GY. Body mass index and adverse outcomes in elderly patients with atrial fibrillation: the AMADEUS trial. *Stroke* 2016;**47**:523–526.
18. Zhu W, Wan R, Liu F, Hu J, Huang L, Li J, Hong K. Relation of body mass index with adverse outcomes among patients with atrial fibrillation: a meta-analysis and systematic review. *J Am Heart Assoc* 2016;**5**:pii: e004006.
19. Proietti M, Guiducci E, Cheli P, Lip GY. Is there an obesity paradox for outcomes in atrial fibrillation? A systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant trials. *Stroke* 2017;**48**:857–866.
20. Rocca B, Fox KAA, Ajjan RA, Andreotti F, Baigent C, Collet JP, Grove EL, Halvorsen S, Huber K, Morais J, Patrono C, Rubboli A, Seljeflot I, Sibbing D, Siegbahn A, Ten Berg J, Vilahur G, Verheugt FWA, Wallentin L, Weiss TW, Wojta J, Storey RF. Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis. *Eur Heart J* 2018;**39**:1672–1686f.
21. Song YM, Sung J, Smith GD, Ebrahim S. Body mass index and ischemic and hemorrhagic stroke—a prospective study in Korean men. *Stroke* 2004;**35**:831–836.
22. Ogunsua AA, Touray S, Lui JK, Ip T, Escobar JV, Gore J. Body mass index predicts major bleeding risks in patients on warfarin. *J Thromb Thrombolysis* 2015;**40**:494–498.
23. Mehta S, Farmer JA. Obesity and inflammation: a new look at an old problem. *Curr Atheroscler Rep* 2007;**9**:134–138.
24. Yu H, Huang Y, Chen X, Nie W, Wang Y, Jiao Y, Reed GL, Gu W, Chen H. High-sensitivity C-reactive protein in stroke patients - The importance in consideration of influence of multiple factors in the predictability for disease severity and death. *J Clin Neurosci* 2017;**36**:12–19.
25. Patel JP, Roberts LN, Arya R. Anticoagulating obese patients in the modern era. *Br J Haematol* 2011;**155**:137–149.
26. Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: effects of weight loss and exercise. *J Am Coll Cardiol* 2017;**70**:2022–2035.
27. Antonopoulos AS, Tousoulis D. The molecular mechanisms of obesity paradox. *Cardiovasc Res* 2017;**113**:1074–1086.
28. Banack HR, Kaufman JS. Does selection bias explain the obesity paradox among individuals with cardiovascular disease? *Ann Epidemiol* 2015;**25**:342–349.
29. Lau DH, Middeldorp ME, Sanders P. Obesity paradox in atrial fibrillation: a distracting reality or fictitious finding? *Eur Heart J* 2016;**37**:2879–2881.
30. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol* 2018;**3**:280–287.
31. Wong CX, Ganesan AN, Selvanayagam JB. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions. *Eur Heart J* 2017;**38**:1294–1302.
32. Packer M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. *J Am Coll Cardiol* 2018;**71**:2360–2372.
33. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-term effect of goal directed weight management in an atrial fibrillation cohort: a long-term follow-up StudY (LEGACY Study). *J Am Coll Cardiol* 2015;**65**:2159–2169.
34. Nalliah CJ, Sanders P, Kottkamp H, Kalman JM. The role of obesity in atrial fibrillation. *Eur Heart J* 2016;**37**:1565–1572.
35. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K; ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.