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FULL RESEARCH PAPER
Arrhythmias

Impact of anthropometric factors on outcomes in atrial fibrillation patients: analysis on 10 220 patients from the European Society of Cardiology (ESC)-European Heart Rhythm Association (EHRA) EurObservational Research Programme on Atrial Fibrillation (EORP-AF) general long-term registry

Giuseppe Boriani [1]*†, Marco Vitolo[1,2,3], Vincenzo L. Malavasi[1], Marco Proietti [2,4,5], Elisa Fantecchi[1], Igor Diemberger [6], Laurent Fauchier [7], Francisco Marin[8], Michael Nabauer[9], Tatjana S. Potpara[10,11], Gheorghe-Andrei Dan[12], Zbigniew Kalarus[13], Luigi Tavazzi[14], Aldo Pietro Maggioni[15], Deirdre A. Lane[2,16], and Gregory Y.H. Lip[2,16]†; on behalf of the ESC-EHRA EORP-AF Long-Term General Registry Investigators‡

[1]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; [2]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; [3]Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy; [4]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [5]Geriatric Unit, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy; [6]Department of Experimental, Diagnostic and Specialty Medicine, Institute of Cardiology, University of Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy; [7]Service de Cardiologie, Centre Hospitalier Universitaire Trousseau, Tours, France; [8]Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, IMIB-Arrixaca, University of Murcia, CIBERCV, Murcia, Spain; [9]Department of Cardiology, Ludwig-Maximilians-University, Munich, Germany; [10]School of Medicine, University of Belgrade, Belgrade, Serbia; [11]Intensive Arrhythmia Care, Cardiology Clinic, Clinical Center of Serbia, Belgrade, Serbia; [12]'Carol Davila' University of Medicine, Colentina University Hospital, Bucharest, Romania; [13]Department of Cardiology, SMDZ in Zabrze, Medical University of Silesia, Katowice, Silesian Centre for Heart Diseases, Zabrze, Poland; [14]Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy; [15]ANMCO Research Center, Firenze, Italy; and [16]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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Aim To investigate the association of anthropometric parameters [height, weight, body mass index (BMI), body surface area (BSA), and lean body mass (LBM)] with outcomes in atrial fibrillation (AF).

Methods and results Ten-thousand two-hundred twenty patients were enrolled [40.3% females, median age 70 (62–77) years, followed for 728 (interquartile range 653–745) days]. Sex-specific tertiles were considered for the five anthropometric variables. At the end of follow-up, survival free from all-cause death was worse in the lowest tertiles for all the anthropometric variables analyzed. On multivariable Cox regression analysis, an independent association with all-cause death was found for the lowest vs. middle tertile when body weight (hazard ratio [HR] 1.66, 95%CI 1.23–2.23), BMI (HR 1.65, 95%CI 1.23–2.21), and BSA

* Corresponding author. Email: giuseppe.boriani@unimore.it
† G.B. and G.Y.H.L. are joint senior authors.
‡ Listed in Appendix.
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(HR 1.49, 95%CI 1.11–2.01) were analysed in female sex, as well as for body weight in male patients (HR 1.61, 95%CI 1.25–2.07). Conversely, the risk of MACE was lower for the highest tertile (vs. middle tertile) of BSA and LBM in males and for the highest tertile of weight and BSA in female patients. A higher occurrence of haemorrhagic events was found for female patients in the lowest tertile of height [odds ratio (OR) 1.90, 95%CI 1.23–2.94] and LBM (OR 2.13, 95%CI 1.40–3.26).

Conclusions In AF patients height, weight, BMI, BSA, and LBM were associated with clinical outcomes, with all-cause death being higher for patients presenting lower values of these variables, i.e. in the lowest tertiles of distribution. The anthropometric variables independently associated with other outcomes were also different between male and female subjects.

Keywords Atrial fibrillation • Body mass index • Lean body mass • Obesity • Outcome • Stroke

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Introduction

Atrial fibrillation (AF) is associated with a wide variety of risk factors, including demographic factors, health behaviours, and other clinical conditions. These associations may create a substrate for the development and maintenance of the arrhythmia, also affecting the tendency towards an evolution from paroxysmal to more advanced forms.[1–10] Several studies have evaluated the relationship between obesity and AF, leading to the intriguing concept of the obesity paradox[11–16] without reducing the important role of weight loss and exercise in AF management, in an integrated approach.[17–19] While higher body mass index (BMI) and obesity attracted major interest, much less attention has been dedicated to other anthropometric variables, such as height and lean body mass (LBM), although more recently they were object of investigation with regard to association with incident AF.[20,21] No data are available from large-scale observational studies on the potential association between a series of anthropometric parameters and outcomes, when measured in the same group of patients with an established diagnosis of clinical AF.

The purpose of our study is to investigate the association of different anthropometric parameters [i.e. weight, height, BMI, body surface area (BSA), and LBM] with outcomes in a large population cohort of unselected patients with AF.

Methods

Study design and cohort

The EURObservational Research Programme on AF (EORP-AF) Long-Term General Registry is a prospective, observational, large-scale multicentre registry, held by the European Society of Cardiology (ESC) and endorsed by the European Heart Rhythm Association (EHRA), enrolling AF patients in current cardiology practices in 250 centres from 27 participating ESC countries. Both in- and outpatients were enrolled consecutively when presenting with AF as primary or secondary.[22–24] The enrolment period was from October 2013 to September 2016. The detailed description of the design and baseline characteristics have been reported previously.[23–25]

Main inclusion criteria were the following: (i) the qualifying AF event had to be recorded by a 12-lead electrocardiogram (ECG), 24 h ECG Holter, or other electrocardiographic documentation within 12 months before enrolment; (ii) age should be 18 years and older; and (iii) written informed consent form. Exclusion criteria were the following: (i) no objective proof of AF; (ii) being previously enrolled in the EORP-AF Pilot Registry; or (iii) being or planned to be enrolled in a pharmacological interventional clinical trial. The study protocol was substantially similar to that of the EORP-AF Pilot Registry reported elsewhere.[26] An institutional review board for every participating institution approved the study protocol. The study was performed according to the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

Thromboembolic risk was defined according to Congestive Heart Failure, Hypertension, Age $\geq$ 75 years, Diabetes Mellitus, Stroke/Transient Ischaemic Attack, Vascular Disease, Age 65–74 years, Sex Category (Female) (CHA_2DS_2-VASc) score.[1,2] Bleeding risk was assessed according to Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile INR, Elderly (>65 years), Drug/Alcohol consumption (HAS-BLED).[1] Symptomatic status was defined according to EHRA score.[1]

For the purpose of our analysis, patients were divided into two subgroups according to male and female sex, in view of the epidemiological differences[27] and the potential different impact on outcomes.[28] We therefore considered five anthropometric parameters including height (cm), weight (kg), BMI (weight/height^2), BSA ($=0.007184 \times \text{height}^{0.725} \times \text{weight}^{0.425}$), and LBM (kg) the latter calculated according to the Boer formula.[29]

All these parameters were analyzed by dividing each of the two populations, male and female, into homogeneous tertiles. All the baseline data [risk factors, cardiovascular (CV) pathologies, comorbidities, and treatments] and the characteristics of AF were reported for each anthropometric data, following this division in tertiles. Patients who had withdrawn consent and those for which complete anthropometric data were not available were not considered.

Follow-up and adverse outcomes

Follow-up was performed at 1 and 2 years after enrollment, both with in office-visit or by phone call or health questionnaires. During follow-up, we recorded the following major adverse clinical events: (i) all-cause deaths; (ii) any haemorrhagic events; (iii) any thromboembolism (TE) (including stroke, transient ischaemic attack, and any peripheral embolism); (iv) any acute coronary syndrome; and (v) CV death.

Investigators reported all available details about incident major adverse clinical events on the centralized electronic case report form.

All-cause death was the primary endpoint of the present analysis. Major adverse cardiovascular events (MACEs, as the composite of the any TE/ACS/CV death according to EORP AF General Long-Term Registry protocol) and any haemorrhagic events (i.e. intracranial bleeding, major bleeding or clinically relevant non-major bleeding) were considered as secondary endpoints.

Statistical analysis

All continuous variables were reported as median and interquartile range (IQR). Among-group comparisons were made using non-parametric

tests, Mann–Whitney *U*, or Kruskal–Wallis test when appropriate. Categorical variables were reported as counts and percentages. Among-group comparisons were made using a χ^2 test or Fisher's exact test, when appropriate.

Plots of Kaplan–Meier curves for all-cause death and MACE according to tertiles were performed. Univariate and multivariable Cox regression analyses were performed to establish the relationship between the various anthropometric data and all-cause death and MACE. All the variables at entry with a *p*-value <0.10 in the univariate analysis and variables considered of relevant clinical interest were included in the multivariable models. We checked the assumption of proportionality by visual inspection and by a comparison with time-dependent covariates. In case of violation of the assumption we replaced the covariate with corresponding time-dependent covariate. The results are presented as hazard ratio (HR), with 95% confidence interval (95% CI).

For haemorrhagic events, since all the specific data to perform a time-to-event data analysis were not available, we used univariate and multivariable logistic regression analyses to evaluate the relationship between anthropometric measures and the occurrence of the outcome. The multivariable model was built by introducing all the variables with a *p*-value <0.10 in the univariate analysis and variables considered of relevant clinical interest. Results are expressed as odds ratio (OR) and 95% CI.

Detection for multicollinearity for each multivariable model was performed through the inspection of variance inflation factor values. No multicollinearity was detected.

The full lists of tested variables in the multivariable analyses (both Cox regression and logistic regression models) are shown in the Supplementary material online.

A two-sided *p*-value <0.05 was considered statistically significant. False discovery rates for the primary outcome (all-cause death) were controlled using Benjamini–Hochberg procedure.

All analyses were performed using SPSS statistical software (IBM Corp. Released 2019. IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp).

Results

From October 2013 to September 2016, 11 096 patients were enrolled in 250 centres from 27 participating European countries, 4512 (40.7%) female; mean age 69 ± 11 years. Overall, 68.5% patients were enrolled in a specialized centre, whereas 52.2% of patients were enrolled in-hospital and 47.8% were enrolled as outpatients.

For the present analysis a final population of 10 220 patients was considered, 6101 males (59.7%) and 4119 females (40.3%). Patient characteristics at baseline, AF characterization and pharmacological treatments at enrolment divided according to sex, are shown in *Table 1*. The most reported AF subtype was permanent AF in both the subgroups (34.7% for males and 34.0% for female patients, respectively), whereas 24.0% of males and 29.4% of female patients had paroxysmal AF.

Hypertension was the most commonly reported comorbidity both in male and female (60.0% and 65.0%, respectively), whereas 2808 patients had a concomitant diagnosis of coronary artery disease, with a greater prevalence in male (32.7%) than in female (23.5%, $p < 0.001$). A concomitant history of heart failure was found in 2535 male patients (41.6%) and 1769 female (42.9%). A previous thromboembolic event (defined as previous stroke, TIA, or systemic embolism) was recorded in 648 male (10.7%) and in 499 female patients (12.3%), while a previous major haemorrhagic event was reported in 292 male patients (4.8%) and 244 (6.0%) females. Among non-cardiac risk factors or comorbidities, chronic kidney disease (CKD) was the most commonly reported (31.4%), with prevalence in female sex (38.8% vs. 26.4%, $p < 0.001$). Overall, median CHA_2DS_2-VASc and median HAS-BLED score were higher in female patients compared to males (*Table 1*).

Anthropometric data

The population, considering separately males and females, were analysed according to distribution into tertiles for the following anthropometric data: height, weight, BMI, BSA, and LBM calculated with the Boer formula. The results in terms of limits of every tertile, median values, and other distribution values are shown in *Table 2*.

The general characteristics of the population, in particular CV risk factors, underlying cardiac disease, comorbidities, and therapies, for every anthropometric variable, according to distribution into tertiles are shown in see Supplementary material online, *Tables S1–S5*.

For any anthropometric variable considered, the lowest tertile of distribution was associated with older age, both in male and female patients. A different distribution of some risk factors and comorbidities was found, with a higher prevalence of hypertension in the highest tertile of weight and BMI for both sexes. For diabetes, the prevalence was higher in the lowest tertile of height, but was higher in the highest tertiles of weight, BMI, BSA, and LBM, for both sexes. For CKD, the prevalence was higher in the lowest tertile of height, BSA, and LBM, both in male and female patients and only in male for weight.

Antithrombotic treatments

Overall, the proportion of patients treated at baseline with oral anticoagulants, considering as indication a $CHA_2DS_2VASc > 0$ in males and >1 in females, was 88.6% (4813/5433) for male patients and 87.1% (3348/3843) for female patients.

Antithrombotic treatments at baseline for male and female patients, according to distribution into tertiles for the analyzed anthropometric factors are shown in see Supplementary material online, *Table S6*. The lowest tertiles of distribution according to weight ($p < 0.001$ for male, $p = 0.013$ for females), BMI ($p < 0.001$ for male, $p = 0.025$ for females), BSA ($p < 0.002$ for male, $p = 0.004$ for females) and LBM ($p = 0.001$ for male, $p = 0.014$ for females) were associated with a relatively higher proportion of patients without antithrombotic therapy (see Supplementary material online, *Table S6*).

Long-term follow-up

Patients were followed for a median of 728 (IQR 653–745) days. At the end of the follow-up, all-cause death occurred in 540 male (9.2%) and 383 female patients (9.7%); MACE in 540 (9.7%) male and 349 (9.4%) female patients, respectively. Haemorrhagic events were reported in 230 (4.1%) male and 150 (4.1%) female patients. Other outcomes are reported in *Table 3*. As shown in *Table 3*, the occurrence of all-cause death and CV death differed significantly according to the distribution in tertiles for the analyzed anthropometric variables, with a higher occurrence in the lowest tertiles of all the anthropometric variables.

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Table 1 Baseline characteristics of the whole population divided in male and female sex

	Whole population $N = 10220$	Male $N = 6101$ (59.7)	Female $N = 4119$ (40.3)	*P*-value M vs. F
Age (years), median (IQR)	70 (62–77)	68 (60–76)	73 (66–79)	<0.001
Age classes, *n* (%)				<0.001
Age <65	3168/10 220 (31.0)	2263/6101 (37.1)	905/4119 (22.0)	
Age 65–74	3439/10 220 (33.6)	2000/6101 (32.8)	1439/4119 (34.9)	
Age ≥ 75	3613/10 220 (35.4)	1838/6101 (30.1)	1775/4119 (43.2)	
Ethnic origin—Caucasian, n (%)	9425/10 211 (92.3)	5690/6096 (93.3)	3735/4115 (90.8)	<0.001
Hypertension, *n* (%)	6286/10 136 (62.0)	3632/6055 (60.0)	2654/4081 (65.0)	<0.001
Diabetes mellitus, *n* (%)	2351/10 160 (23.1)	1353/6064 (22.3)	998/4096 (24.4)	0.016
Smoking (current), *n* (%)	908/9530 (9.5)	702/5681 (12.4)	206/3849 (5.4)	<0.001
No physical activity, *n* (%)	3720/10 219 (36.4)	1888/6101 (30.9)	1832/4118 (44.5)	<0.001
Lipid disorder, *n* (%)	4071/9810 (41.5)	2414/5868 (41.1)	1657/3942 (42.0)	0.38
HF history, *n* (%)	4304/10 220 (42.1)	2535/6101 (41.6)	1769/4119 (42.9)	0.16
CAD, *n* (%)	2808/9661 (29.1)	1907/5832 (32.7)	901/3829 (23.5)	<0.001
Valvular disease, *n* (%)	2361/10 021 (23.6)	1274/6002 (21.2)	1087/4019 (27.0)	<0.001
Dilated CMP, *n* (%)	861/10 107 (8.5)	675/6044 (11.2)	186/4063 (4.6)	0.001
Hypertrophic CMP, *n* (%)	310/10 099 (3.1)	169/6036 (2.8)	141/4063 (3.5)	0.06
Restrictive CMP, *n* (%)	19/10 217 (0.2)	11/6100 (0.2)	8/4117 (0.2)	0.29
PAH, *n* (%)	707/10 217 (6.9)	349/6100 (5.7)	358/4117 (8.7)	<0.001
Previous TE events, *n* (%)	1147/10 126 (11.3)	648/6058 (10.7)	499/4068 (12.3)	0.015
Previous ischaemic stroke, *n* (%)	605/10 218 (5.9)	352/6101 (5.8)	253/4117 (6.1)	0.020
Previous TIA, *n* (%)	310/10 218 (3.0)	170/6101 (2.8)	140/4117 (3.4)	0.006
Previous PE/DVT, *n* (%)	209/10 218 (2.0)	108/6101 (1.8)	101/4117 (2.5)	0.002
Previous haemorrhagic events, *n* (%)	536/10 119 (5.3)	292/6049 (4.8)	244/4070 (6.0)	0.010
Peripheral vascular disease, *n* (%)	799/10 003 (8.0)	497/5981 (8.3)	302/4022 (7.5)	0.15
Liver disease, *n* (%)	285/10 161 (2.8)	173/6067 (2.9)	112/4094 (2.7)	0.73
COPD, *n* (%)	903/10 145 (8.9)	585/6061 (9.7)	318/4084 (7.8)	0.001
Dementia, *n* (%)	129/10 181 (1.3)	60/6080 (1.0)	69/4101 (1.7)	0.002
Anaemia, *n* (%)	524/10 187 (5.1)	248/6081 (4.1)	276/4106 (6.7)	<0.001
Malignancy (current + prior), *n* (%)	755/10 219 (7.3)	412/6101 (6.7)	343/4118 (8.3)	0.003
CKD, *n* (%)	3210/10 200 (31.4)	1612/6101 (26.4)	1598/4119 (38.8)	<0.001
LVEF (%), median (IQR)	55 (45–62)	55 (44–61)	58 (50–63)	<0.001
GFR (CKD-EPI) (ml/min/1.73m^2), median (IQR)	69 (53–84)	73 (58–87)	64(49–80)	<0.001
GFR (Cockroft Gault) (ml/min), median (IQR)	74 (55–97)	82 (61–105)	65 (48–85)	<0.001
CHA_2DS_2VASc, median (IQR)	3 (2–4)	2 (1–4)	4 (3–5)	<0.001
HASBLED, median (IQR)	1 (1–2)	1 (1–2)	2 (1–2)	<0.001
CHA_2DS_2VASc >0 M, > 1 F, *n* (%)	9280/10 212 (90.9)	5434/6097 (89.1)	3846/4115 (93.5)	<0.001
HASBLED ≥ 3, *n* (%)	1751/10 220	1040/6101 (17.0)	711/4119 (17.3)	0.77
AF type, *n* (%)				
Paroxysmal	2631/10 055 (26.2)	1436/5993 (24.0)	1195/4062 (29.4)	<0.001
Persistent	1961/10 055 (19.5)	1270/5993 (21.2)	691/4062 (17.0)	<0.001
Permanent	3463/10 055 (34.4)	2081/5993 (34.7)	1382/4062 (34.0)	0.41
Long-standing persistent	449/10 055 (4.5)	294/5993 (4.9)	155/4062 (3.8)	0.02
First diagnosed	1551/10 055 (15.4)	912/5993 (15.2)	639/4062 (15.7)	0.48
EHRA score, median (IQR)	2 (1–2)	2 (1–2)	2(1–2)	<0.001
Pharmacological management				
Any antiarrhythmic treatment, *n* (%)	2846/10 210	1734/6097 (28.4)	1112/4113 (27.0)	0.12
ACE-inhibitors, *n* (%)	4288/10 211 (42.0)	2683/6098 (44.0)	1605/4113 (39.0)	<0.001
ARBs, *n* (%)	1992/10 208 (19.5)	1062/6096 (17.4)	930/4112 (22.6)	<0.001
Beta-blockers, *n* (%)	7014/10 213 (68.7)	4147/6098 (68.0)	2867/4115 (69.7)	0.19
Digoxin, *n* (%)	1458/10 209 (14.3)	777/6096 (12.7)	681/4113 (16.6)	<0.001

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Table 1 *Continued*

	Whole population $N = 10220$	Male $N = 6101$ (59.7)	Female $N = 4119$ (40.3)	*P*-value M vs. F
Diuretics, *n* (%)	5188/10 210 (50.8)	2965/6097 (48.6)	2223/4113 (54.0)	<0.001
Aldosterone blockers, *n* (%)	1799/10 209 (17.6)	1065/6096 (17.5)	734/4113 (17.8)	0.84
DHP—CCB, *n* (%)	1703/10 211 (16.7)	974/6097 (16.0)	729/4114 (17.7)	0.07
Non-DHP—CCB, *n* (%)	547/10 210 (5.4)	282/6096 (4.6)	265/4114 (6.4)	<0.001
Statins, *n* (%)	4316/10 211 (42.3)	2676/6098 (43.9)	1640/4113 (39.9)	<0.001

ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blockers, CKD, chronic kidney disease; CMP, cardiomyopathy; COPD,chronic obstructive pulmonary disease; DHP, Dihydropyridine; EHRA,European Heart Rate Association; F, females; GFR, glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; M, males; n, number; PAH, pulmonary artery hypertension; TIA, transient ischaemic attack; TE, thromboembolic.

Kaplan–Meier curves showed that survival free from all-cause death (*Figure 1A and B*) was significantly different according to tertiles of all the anthropometric variables, being worse for patients in the lowest tertiles, as compared with both the middle and the highest tertile, for male patients. For female sex, the survival from all-cause death was similar for the middle and highest tertiles, for all the anthropometric variables that were considered, while it was worse for the lowest tertiles for all anthropometric variables. On multivariable Cox regression analysis, a significant association between anthropometric factors and mortality was confirmed, in terms of significantly increased risk, for the lowest tertile of weight in males and for the lowest tertiles of weight, BMI and BSA in female patients (*Figure 2*). The other variables significantly associated with mortality are shown in see Supplementary material online, *Tables S7 and S8* and included age, heart failure, CKD, and anaemia for both sexes.

Kaplan–Meier curves showed that for survival free from MACE (any TE, any ACS, or CV death), the highest tertile had the most favorable outcome, but differences vs. the other tertiles varied according to the anthropometric variables taken into account. In male patients, outcome differences were more evident when BSA and LBM were considered (see Supplementary material online, *Figure S1A*).

For female patients, the better outcome for the highest tertile was confirmed only when weight, BSA, and LBM were considered (see Supplementary material online, *Figure S1B*). At the multivariable Cox regression analysis, a significant association between anthropometric factors and MACE was found in terms of lower risk for the highest tertile of BSA and LBM for male patients, while for female subjects a lower risk for the highest tertile was found for weight and BSA (see Supplementary material online, *Figure S2*, top panels). The other variables significantly associated with MACE are shown in Supplementary material online, *Tables S9 and S10* and included heart failure and CKD for both sexes, as well as age and CAD in male patients.

The multivariable logistic regression analysis for haemorrhagic events (see Supplementary material online, *Figure S2*, bottom panels, *Tables S11 and S12*) showed for males no differences according to tertiles of the anthropometric variables, while for female patients, the lowest tertiles of height and LBM were associated with a higher occurrence of haemorrhagic events.

Discussion

The present study is derived from a European prospective registry based on voluntary participation that enrolled more than 11 000 patients in 250 centres from 27 countries across Europe. The analysis evaluated a series of anthropometric variables examining the association with patient clinical profile at baseline and the implications for long-term outcome according to the distribution in tertiles, for male and female patients, respectively.

Our study shows that in AF patients, height, weight, BMI, BSA, and LBM are associated with clinical outcomes, with all-cause death being higher for patients presenting lower values of these variables, i.e. in the lowest tertiles of distribution. Moreover, the anthropometric variables independently associated with other outcomes differ between male and female subjects.

While previous papers in the literature were focused on the relationship between anthropometric variables and incident AF,[20,30–32] no detailed information is available, in comparative terms, on the relationship between anthropometric factors and outcome in patients with clinical AF. Additionally, none of the previous large scale registries considered up to now the outcome implications of a series of anthropometric factors assessed in the same cohort. Moreover, several studies on the outcome of AF patients were derived from multicentre studies including patients from different continents with different ethnicities thus conditioning major differences in patients profiles and anthropometric variables according to ethnicities.[33,34]

The present study is the first focused on the relationship between anthropometric variables and outcome in European AF patients. Our results showed that patient profile at baseline assessment is substantially different in terms of risk factors and comorbidities when patients are classified according to tertiles of weight, BMI, BSA, and LBM, with important clinical implications for long-term outcome, especially in terms of all cause death, for both sexes. The analysis, based on specific anthropometric factors of easy assessment in daily practice, was done separately according to sex, since some reports suggest that for incident AF the presence of obesity and severe obesity are associated with increased risk of AF, but with an interaction between sex and BMI.[35]

Our study is original in evaluating a series of variables, such as BMI, BSA, and LBM, that can describe the anthropometric profile through a simple assessment in practice, since they were all derived from height and weight. In literature, most of the studies were focused

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Table 2 Distribution according to tertiles for anthropometric data, in male and female patients

	Male		
	Lowest tertile	**Middle tertile**	**Highest tertile**
Height (cm)	<172	172–178	>178
Median; IQR; min–max	164; 160–168;140–171	175; 173–177; 172–178	183; 180–186; 179–210
Weight (kg)	<80	80–90	>90
Median; IQR; min–max	70; 63–75; 33–79	85; 81–88; 80–90	100; 95–110; 91–205
BMI (kg/m^2)	<25.8	25.8–29.4	>29.4
Median; IQR; min–max	23.8; 22.2–24.8; 13.6–25.7	27.5; 26.6–28.4; 25.8–29.4	32.7; 31.0–35.5; 29.5–64.4
BSA (m^2)	<1.90	1.90–2.10	>2.10
Median; IQR; min–max	1.77; 1.67–1.85; 1.23–1.92	1.99; 1.95–2.03; 1.92–2.08	2.19; 2.13–2.28; 2.10–3.02
LBM (kg)	<59.4	59.4–65.5	>65.5
Median; IQR; min–max	49.9; 45.2–54.9; 28.0–59.4	62.2; 60.9–63.7; 59.4–65.5	70.1; 67.5–73.9; 65.5–113.6
	Female		
	Lowest tertile	**Middle tertile**	**Highest tertile**
Height (cm)	<160	160–164	>164
Median; IQR; min–max	155; 152–158; 140–159	162; 160–163; 160–164	175; 170–180; 165–210
Weight (kg)	<67	67–80	>80
Median; IQR; min–max	60; 56–64; 33–66	73; 70–76; 67–79	90; 90–100; 80–205
BMI (kg/m^2)	<25.5	25.5–29.9	>29.9
Median; IQR; min–max	23.7; 22.2–24.7; 13.6–25.5	27.5; 26.5–28.7; 25.6–29.9	33.0; 31.2–35.8; 30.0–64.0
BSA (m^2)	<1.70	1.70–1.85	>1.85
Median; IQR; min–max	1.61; 1.55–1.66; 1.23–1.68	1.78; 1.74–1.81; 1.70–1.84	2.01; 1.93–2.14; 1.86–3.02
LBM (kg)	<44.90	44.90–49.40	>49.4
Median; IQR; min–max	41.8; 39.6–43.5; 28.8–44.9	47.2; 46.1–48.3; 44.9–49.4	60.9; 55.6–66.6; 49.4–113.6

BMI, body mass index; BSA, body surface area; IQR, interquartile range; LBM, lean body mass.

on BMI or weight.[36] While assessment of BSA does not seem to add striking clinical hints over BMI, LBM appears of interest since it may be the expression of a lower muscular mass which in terms of muscular strength may reflect patient frailty.[37–40]

The findings of our study show that anthropometric factors are associated with patient outcomes, with a higher occurrence of death in the lowest tertiles of all the variables. However, major differences in patient profile and comorbidities among the tertiles have to be considered. Using the multivariable Cox regression indeed, only weight was found significantly associated with death in both male and female subjects. Our study highlights that low body weight is associated with adverse outcomes, suggesting that also in AF there is evidence of the association between underweight and worse outcomes, as reported for the general population[41,42] and in patients with previous history of CV disease.[43] We found that patients with low body weight, particularly male patients, have a higher prevalence of chronic diseases (such as heart failure, coronary artery disease, valvular heart disease, CKD, peripheral artery disease, chronic obstructive pulmonary disease, and dementia), and therefore they appear to be characterized by a variable combination of aging, clinical complexity frailty and multimorbidity. These findings expand previous studies available in literature,[37,38,44–46] suggesting the need for coordinated and integrated care, in a multidisciplinary setting.[25,47]

Moreover, our study adds to current knowledge that the adverse outcomes related to specific anthropometric profiles are not limited to very low body weight, but extend to the lower tertiles of others anthropometric variables, with some differences between sex. It is noteworthy that the association between low body weight and mortality was found even after adjusting for the use of antithrombotic treatments, indicating that this association goes beyond the well-known association between low body weight and bleeding.[11,48]

Stratification of the population according to BMI, a variable categorized in defined classes according to WHO, showed that in our cohort the lowest tertile included patient with a normal BMI, the middle tertile patients with overweight and the upper tertile patients with obesity, thus indicating that in Europe the prevalence of overweight/obesity is consistent, appearing even higher among AF patients as compared to what reported for middle age European subjects.[49]

The prevalence of obesity is increasing worldwide and in recent years increasing evidence indicate that overweight and obesity are associated with higher incidence, prevalence, severity, and progression of AF as compared with normal weight subjects.[12,50] This has led to consider weight control as a key component of an integrated approach to AF management[1,47,51] in order to improve AF care. With regard to outcome in AF patients with obesity, many contributions in literature analysed the controversial concept of the obesity

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Table 3 Outcomes at the end of follow-up for male and female patients according to anthropometric data

		Lowest tertile	Middle tertile	Highest tertile	Total	*P*-value
Male						
Height						
	All-cause death, *n* (%)	204/1686 (12.1)	200/2170 (9.2)	136/2022 (6.7)	540/5878 (9.2)	<0.001[a]
	MACE, *n* (%)	206/1627 (12.7)	204/2071 (9.9)	130/1878 (6.9)	540/5576 (9.7)	<0.001
	Any TE, *n* (%)	36/1615 (2.2)	44/2065 (2.1)	41/1873 (2.2)	121/5553 (2.2)	0.98
	Any ACS, *n* (%)	97/1620 (6.0)	103/2065 (5.0)	52/1874 (2.8)	252/5559 (4.5)	<0.001
	Stroke/TIA, *n* (%)	27/1686 (1.6)	35/2170 (1.6)	28/2022 (1.4)	90/5878 (1.5)	0.80
	CV death, *n* (%)	88/1624 (5.4)	73/2071 (3.5)	45/1876 (2.4)	206/5571 (3.7)	<0.001
	Haemorrhagic events, *n* (%)	84/1615 (5.2)	88/2062 (4.3)	58/1872 (3.1)	230/5549 (4.1)	0.008
Weight						
	All-cause death, *n* (%)	254/1894 (13.4)	157/1910 (8.2)	129/2074 (6.2)	540/5878 (9.2)	<0.001[a]
	MACE, *n* (%)	218/1813 (12.0)	182/1791 (10.2)	140/1972 (7.1)	540/5576 (9.7)	<0.001
	Any TE, *n* (%)	40/1802 (2.2)	44/1784 (2.5)	37/1967 (1.9)	121/5553 (2.2)	0.47
	Any ACS, *n* (%)	89/1806 (4.9)	88/1785 (4.9)	75/1968 (3.8)	252/5559 (4.5)	0.16
	Stroke/TIA, *n* (%)	33/1894 (1.7)	33/1910 (1.7)	24/2074 (1.2)	90/5878 (1.5)	0.23
	CV death, *n* (%)	106/1811 (5.9)	60/1790 (3.4)	40/1970 (2.0)	206/5571 (3.7)	<0.001
	Haemorrhagic events, *n* (%)	87/1802 (4.8)	70/1782 (3.9)	73/1965 (3.7)	230/5549 (4.1)	0.19
BMI						
	All-cause death, *n* (%)	229/1894 (12.1)	173/2035 (8.5)	138/1949 (7.1)	540/5878 (9.2)	<0.001[a]
	MACE, *n* (%)	202/1784 (11.3)	185/1923 (9.6)	153/1869 (8.2)	540/5576 (9.7)	0.006
	Any TE, *n* (%)	44/1774 (2.5)	42/1913 (2.2)	35/1866 (1.9)	121/5553 (2.2)	0.46
	Any ACS, *n* (%)	76/1779 (4.3)	96/1914 (5.0)	80/1866 (4.3)	252/5559 (4.5)	0.46
	Stroke/TIA, *n* (%)	34/1894 (1.8)	34/2035 (1.7)	22/1949 (1.1)	90/5878 (1.5)	0.19
	CV death, *n* (%)	97/1782 (5.4)	61/1920 (3.2)	48/1869 (2.6)	206/5571 (3.7)	<0.001
	Haemorrhagic events, *n* (%)	79/1774 (4.5)	76/1910 (4.0)	75/1865 (4.0)	230/5549 (4.1)	0.73
BSA						
	All-cause death, *n* (%)	232/1784 (13.0)	188/1951 (9.6)	120/2143 (5.6)	540/5878 (9.2)	<0.001[a]
	MACE, *n* (%)	210/1713 (12.3)	199/1837 (10.8)	131/2026 (6.5)	540/5576 (9.7)	<0.001
	Any TE, *n* (%)	35/1704 (2.1)	49/1826 (2.7)	37/2023 (1.8)	121/5553 (2.2)	0.17
	Any ACS, *n* (%)	96/1708 (5.6)	83/1827 (4.5)	73/2024 (3.6)	252/5559 (4.5)	0.013
	Stroke/TIA, *n* (%)	28/1784 (1.6)	40/1951 (2.1)	22/2143 (1.0)	90/5878 (1.5)	0.028
	CV death, *n* (%)	94/1710 (5.5)	80/1837 (4.4)	32/2024 (1.6)	206/5571 (3.7)	<0.001
	Haemorrhagic events, *n* (%)	91/1703 (5.3)	74/1824 (4.1)	65/2022 (3.2)	230/5549 (4.1)	0.005
LBM						
	All-cause death, *n* (%)	247/1920 (12.9)	176/1917 (9,2)	117/2041 (5.7)	540/5878 (9.2)	<0.001[a]
	MACE, *n* (%)	224/1846 (12.1)	194/1801 (10.8)	122/1929 (6.3)	540/5576 (9.7)	<0.001
	Any TE, *n* (%)	41/1834 (2.2)	47/1793 (2.6)	33/1926 (1.7)	121/5553 (2.2)	0.16
	Any ACS, *n* (%)	100/1838 (5.4)	83/1794 (4.6)	69/1927 (3.6)	252/5559 (4.5)	0.023
	Stroke/TIA, *n* (%)	34/1920 (1.8)	37/1917 (1.9)	19/2041 (0.9)	90/5878 (1.5)	0.22
	CV death, *n* (%)	99/1843 (5.4)	76/1801 (4.2)	31/1927 (1.6)	206/5571 (3.7)	<0.001
	Haemorrhagic events, *n* (%)	96/1833 (5.2)	71/1791 (4.0)	63/1925 (3.3)	230/5549 (4.1)	0.009
Female						
Height						
	All-cause death, *n* (%)	145/1179 (12.3)	113/1196 (9.4)	125/1570 (8.0)	383/3945 (9.7)	<0.001[a]
	MACE, *n* (%)	121/1131 (10.7)	111/1118 (9.9)	117/1453 (8.1)	349/3702 (9.4)	0.058
	Any TE, *n* (%)	28/1121 (2.5)	26/1112 (2.3)	40/1449 (2.8)	94/3682 (2.6)	0.79
	Any ACS, *n* (%)	47/1122 (4.2)	45/1113 (4.0)	48/1452 (3.3)	140/3687 (3.8)	0.45
	Stroke/TIA, *n* (%)	25/1179 (2.1)	17/1196 (1.4)	31/1570 (2.0)	73/3945 (1.9)	0.40
	CV death, *n* (%)	53/1129 (4.7)	49/1117 (4.4)	40/1450 (2.8)	142/3696 (3.8)	0.021
	Haemorrhagic events, *n* (%)	67/1122 (6.0)	34/1112 (3.1)	49/1448 (3.4)	150/3682 (4.1)	0.001
Weight						

Continued

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Table 3 *Continued*

		Lowest tertile	Middle tertile	Highest tertile	Total	*P*-value
	All-cause death, *n* (%)	173/1226 (14.1)	107/1324 (8.1)	103/1395 (7.4)	383/3945 (9.7)	<0.001[a]
	MACE, *n* (%)	120/1161 (10.3)	127/1237 (10.3)	102/1304 (7.8)	349/3702 (9.4)	0.048
	Any TE, *n* (%)	25/1150 (2.2)	39/1230 (3.2)	30/1302 (2.3)	94/3682 (2.6)	0.24
	Any ACS, *n* (%)	40/1152 (3.5)	59/1233 (4.8)	41/1302 (3.1)	140/3687 (3.8)	0.077
	Stroke/TIA, *n* (%)	21/1226 (1.7)	31/1324 (2.3)	21/1395 (1.5)	73/3945 (1.9)	0.25
	CV death, *n* (%)	69/1158 (6.0)	38/1234 (3.1)	35/1304 (2.7)	142/3696 (3.8)	<0.001
	Haemorrhagic events, *n* (%)	52/1151 (4.5)	52/1230 (4.2)	46/1301 (3.5)	150/3682 (4.1)	0.44
BMI						
	All-cause death, *n* (%)	165/1309 (12.6)	116/1293 (9.0)	102/1343 (7.6)	383/3945 (9.7)	<0.001[a]
	MACE, *n* (%)	125/1232 (10.1)	106/1195 (8.9)	118/1275 (9.3)	349/3702 (9.4)	0.54
	Any TE, *n* (%)	32/1221 (2.6)	29/1189 (2.4)	33/1272 (2.6)	94/3682 (2.6)	0.95
	Any ACS, *n* (%)	45/1223 (3.7)	48/1192 (4.0)	47/1272 (3.7)	140/3687 (3.8)	0.88
	Stroke/TIA, *n* (%)	27/1309 (2.1)	22/1293 (1.7)	24/1343 (1.8)	73/3945 (1.9)	0.77
	CV death, *n* (%)	64/1229 (5.2)	36/1192 (3.0)	42/1275 (3.3)	142/3696 (3.8)	0.009
	Haemorrhagic events, *n* (%)	54/1222 (4.4)	43/1189 (3.6)	53/1271 (4.2)	150/3682 (4.1)	0.59
BSA						
	All-cause death, *n* (%)	179/1205 (14.9)	99/1290 (7.7)	105/1450 (7.2)	383/3945 (9.7)	<0.001[a]
	MACE, *n* (%)	128/1147 (11.2)	118/1206 (9.8)	103/1349 (7.6)	349/3702 (9.4)	0.010
	Any TE, *n* (%)	26/1133 (2.3)	37/1202 (3.1)	31/1347 (2.3)	94/3682 (2.6)	0.37
	Any ACS, *n* (%)	45/1136 (4.0)	53/1203 (4.4)	42/1349 (3.1)	140/3687 (3.8)	0.22
	Stroke/TIA, *n* (%)	21/1205 (1.7)	31/1290 (2.4)	21/1450 (1.4)	73/3945 (1.9)	0.17
	CV death, *n* (%)	70/1143 (6.1)	38/1205 (3.2)	34/1348 (2.5)	142/3696 (3.8)	<0.001
	Haemorrhagic events, *n* (%)	59/1134 (5.2)	44/1202 (3.7)	47/1346 (3.5)	150/3682 (4.1)	0.06
LBM						
	All-cause death, *n* (%)	183/1288 (14.2)	100/1293 (7.7)	100/1364 (7.3)	383/3945 (9.7)	<0.001[a]
	MACE, *n* (%)	135/1229 (11.0)	115/1209 (9.5)	99/1264 (7.8)	349/3702 (9.4)	0.026
	Any TE, *n* (%)	30/1217 (2.5)	27/1202 (2.2)	37/1263 (2.9)	94/3682 (2.6)	0.54
	Any ACS, *n* (%)	50/1219 (4.1)	50/1204 (4.2)	40/1264 (3.2)	140/3687 (3.8)	0.35
	Stroke/TIA, *n* (%)	24/1288 (1.9)	23/1293 (1.8)	26/1364 (1.9)	73/3945 (1.9)	0.97
	CV death, *n* (%)	68/1226 (5.5)	45/1207 (3.7)	29/1263 (2.3)	142/3696 (3.8)	<0.001
	Haemorrhagic events, *n* (%)	74/1218 (6.1)	37/1202 (3.1)	39/1262 (3.1)	150/3682 (4.1)	<0.001

ACS, acute coronary syndrome; BMI, body mass index; BSA, body surface area; CV, cardiovascular; LBM, lean body mass; MACE, major adverse cardiovascular events (composite of any TE, any ACS, and/or CV death); n, numbers; TIA, transient ischaemic attack; TE, thromboembolism.
[a]Adjusted *P*-values after Benjamini–Hochberg procedure.

paradox, already reported in several CV disease state. Although obesity is an important CV risk factor in the general population, it has been reported that patients with established CV disease and an elevated BMI experience better outcomes than patients with a normal BMI.[13,52] The analysis performed in the present study was not focused on this debated and intriguing concept[11,12] since we considered the distribution in tertiles of our European patients and we enlarged the interest to other anthropometric variables. Indeed, some of our findings are compatible with an obesity paradox, although much more evident when weight rather than BMI was considered. It is noteworthy that on multivariable Cox analysis, a high BMI was associated with better outcomes in female but not in male patients, in full agreement with the findings of a previous EORP registry, with a much smaller patient sample (EORP AF Pilot study),[28] suggesting that the limitations in approaching obesity using BMI, which is an imperfect measure of adiposity, may have a different impact on outcomes between male and female AF patients.

Although BMI indicates overweight relative to height, it does not discriminate between fat mass and LBM.[53,54] This constitutes one of the many reservations that are associated with the concept of the obesity paradox. When MACE were analysed, BMI and weight were not significantly associated with the outcome at multivariable Cox analysis, indicating the complex factors involved in the assessment of the obesity paradox.[55]

While underweight accounts for only few patients among European countries (2% in middle age subjects according to a recent survey),[49] the lowest tertiles of weight and BMI were found associated with an increased risk of death, that according to the multivariate analysis, was also expression of the contribution of comorbidities. In two studies related to Asian population, an increased risk for patients with low body weight (<60 kg or underweight (BMI < 18.5 kg/m^2) has been previously highlighted.[56,57] Our study suggests that even the lowest tertiles of weight, corresponding in our European cohort to weights below 80 and 67 kg

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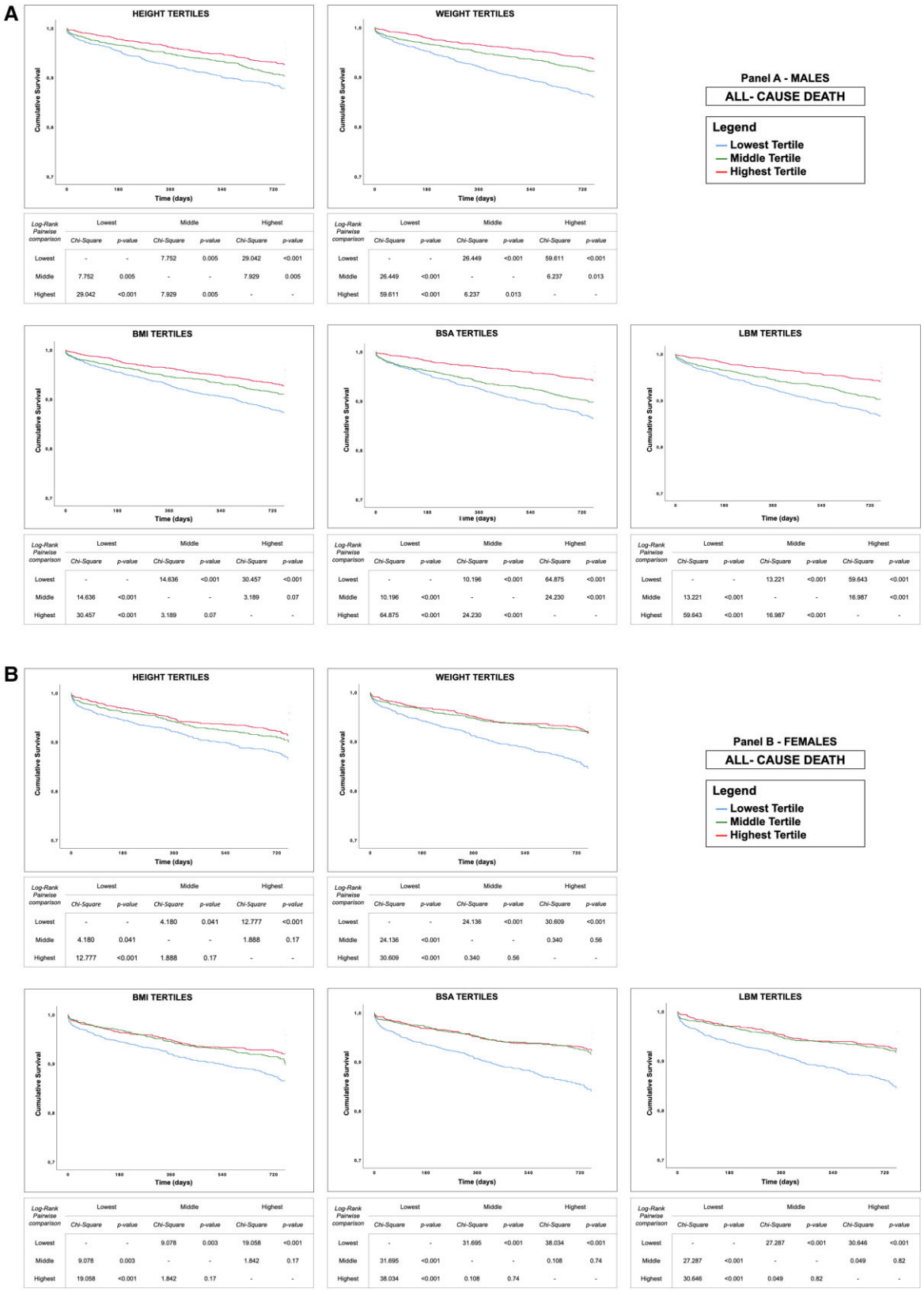

Figure 1 Kaplan–Meier curves for all-cause death in male (*A*) and female patients (*B*) according to anthropometric data. BMI, body mass index; BSA, body surface area; LBM, lean body mass.

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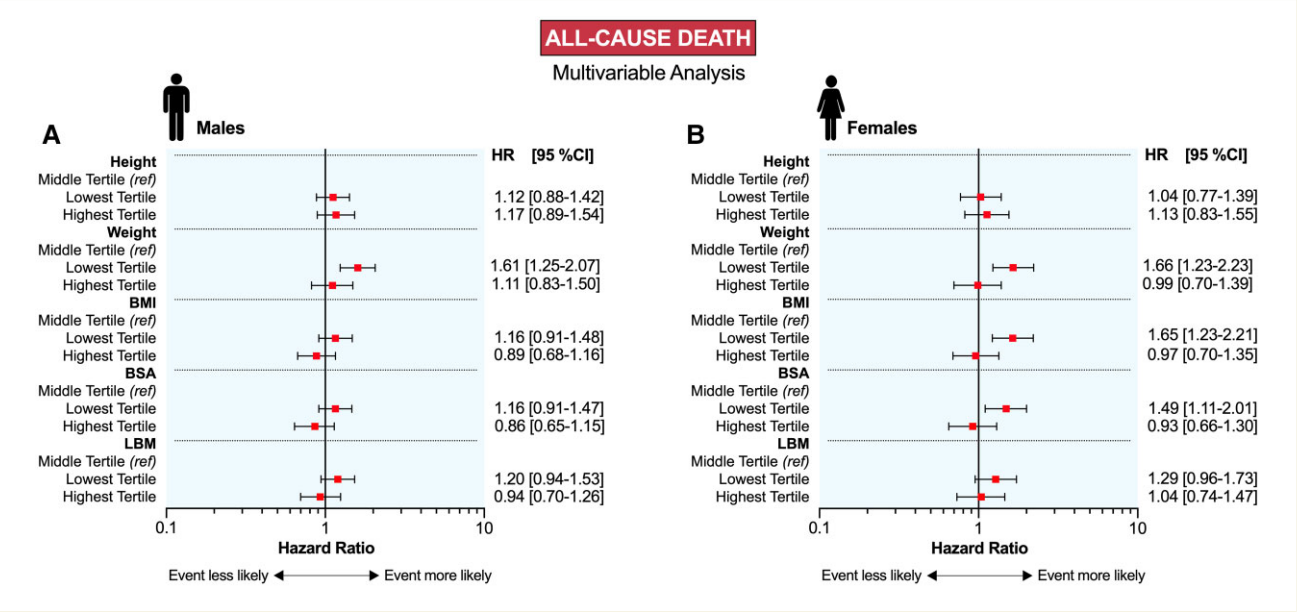

Figure 2 Multivariable Cox regression analysis for all-cause death in male (*A*) and female patients (*B*) with regard to tertiles of anthropometric data. The full results of the Cox regression analysis are shown in see Supplementary material online, *Tables S7 and S8*. BMI, body mass index; BSA, body surface area; CI, confidence interval; IQR, interquartile range; LBM, lean body mass; HR, hazard ratio; ref, reference.

in male and female patients, respectively, are exposed to a higher risk of death as compared to the middle tertile.

These findings indicate the need to adhere to the recommendations for integrated care included in 2020 ESC AF guidelines,[1,25,58] especially for patients with the lowest values of anthropometric factors, who have a more complex profile in terms of age, comorbidities and predicted outcome for death and MACE. Our data with regard to MACE indicate that in a population of AF patients with a high proportion of patients treated with anticoagulants, outcome events are dominated by all-cause death, with a relatively low rate of stroke events.

A higher occurrence of haemorrhagic events was found for female patients in the lowest tertiles of height. This constitutes a novel finding extending to the setting of patients with AF treated with oral anticoagulants what previously found in a community study in terms of a an increased risk of haemorrhagic stroke in female subjects with an inverse association with stature.[59]

This finding, despite it needs to be confirmed in further studies, suggests a more careful patient surveillance for the risk of bleeding in patients with low stature. In our study the lowest tertile of LBM in female subjects was associated with an increased haemorrhagic risk. The evaluation of LBM deserves interest, since for AF incidence, an high LBM may be more important than the fat tissue in conditioning the risk of AF development.[20,60,61]

In a large Danish registry cohort, where LBM was measured at baseline to obtain fat and LBM estimates, LBM was the predominant anthropometric risk factor for AF development at long term, whereas no association was observed for either of the obesity-related anthropometric measures after adjustment for LBM.[20] Although for LBM, the assessment with bioelectrical impedance or dual-energy X-ray absorptiometry, may provide a more accurate assessment of body composition, the advantage of our analysis is that LBM was derived from standard parameters according to Boer's formula.[29] This may offer potentially useful additional information on AF management and outcome prediction on a series of anthropometric variables, of easy assessment at bedside. This is in line with the perspective of an integrated and more personalized approach to patients with AF.[1,25]

Study limitations

Our study has inherent limitations. In view of the observational nature of our study, we cannot exclude the effect of residual confounding, and our results should be considered to be hypothesis-generating. Despite the multivariable models were adjusted for several variables, given the observational nature of the study, our findings have to be interpreted in terms of associations and may be affected by confounding.

The analysis that we performed was based on data collected at baseline and did not take into account changes in body weight during follow-up. Moreover, the assessment of different aspects of body habitus has to consider the inter-relationships between anthropometric variables, but we evaluated the association between each anthropometric variable and outcome independently on the other anthropometric variables. A specific limitation of our analysis relies in the calculation of the LBM. We did not measure LBM through bioelectrical impedance-derived measures but we used the Boer equation[29] which was derived from studies in healthy subjects. Despite clinical height- and weight-based formulae may be used in clinical practice, the Boer formula has been reported to be less accurate as compared to imaging/impedance modalities, such as dual-energy x-ray absorptiometry computed tomography (CT) or positron emission tomography (PET)/CT scans. We have to recognize that in view of these limitations LBM is less used in clinical practice, as compared to the other anthropometric variables evaluated in this analysis.

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Conclusions

Anthropometric factors, such as height, weight, BMI, BSA, and LBM (calculated with the Boer formula) are associated with important differences in patient's profile with regard to risk factors and co-morbidities, with a clinical value that goes beyond their epidemiological significance. Moreover, these anthropometric variables are associated with outcomes, with a higher occurrence of death in the lowest tertiles for all the anthropometric variables considered, with differences among male and female subjects. A higher occurrence of haemorrhagic events was found for female patients in the lowest tertiles of height and in the lowest tertile of LBM, suggesting further research in the field, since LBM has not been object of studies on outcome in patients with AF.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Data availability

The data underlying this article were provided by the European Society of Cardiology with permission. Data will be shared on request to the corresponding author with permission of ESC Editorial is also expected but not yet confirmed.

Appendix

EURObservational Research Programme Atrial Fibrillation (EORP-AF) Long-Term General Registry Committees and Investigators

Executive committee: G.Boriani (Chair), G.Y.H. Lip, L. Tavazzi, A. P. Maggioni, G-A. Dan, T. Potpara, M. Nabauer, F. Marin, Z. Kalarus, L. Fauchier.

Steering Committee (National Coordinators): A. Goda, University Hospital Center "Mother Tereza", Tirana, Albania; G. Mairesse, Cliniques du Sud-Luxembourg, Arlon, Belgium; T. Shalganov, National Heart Hospital, Sofia, Bulgaria; L. Antoniades, Nicosia General Hospital, Latsia, Cyprus; M. Taborsky, University Hospital Olomouc, Olomouc, Czech Republic; S. Riahi, Aalborg University Hospital, Aalborg, Denmark; P. Muda, University of Tartu, Tartu, Estonia; I. García Bolao, Navarra Institute for Health Research, Pamplona, Spain; O. Piot, Centre Cardiologique du Nord, Saint-Denis, France; M. Nabauer, Ludwig-Maximilians-University, Munich, Germany; K. Etsadashvili, G. Chapidze Emergency Cardiology Center, Tbilisi, Georgia; EN. Simantirakis, University Hospital of Heraklion, School of Medicine, University of Crete, Heraklion, Crete, Greece; M. Haim, Soroka Medical Center, Beer Sheva, Israel; A. Azhari, J. Najafian, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; M. Santini, San Filippo Neri Hospital, Rome, Italy; E. Mirrakhimov, National Center of Cardiology and Internal Medicine, Bishkek, Kyrgyzstan; K. Kulzida, Scientific-Research Institute of Cardiology and Internal Diseases, Almaty, Republic of Kazakhstan; A. Erglis, Pauls Stradins Clinical University Hospital University of Latvia Riga Latvia; L. Poposka, University Clinic of Cardiology, Faculty of Medicine, Ss Cyril and Methodius University of Skopje, Skopje, Republic of Macedonia; MR. Burg, Mater Dei Hospital, Triq Dun Karm Psaila, Malta; H. Crijns, Ö. Erküner, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands; D. Atar, Oslo University Hospital Ullevål and Institute of Clinical Sciences, University of Oslo, Oslo, Norway; R. Lenarczyk, Silesian Center for Heart Disease, Zabrze, Poland; M. Martins Oliveira, Hospital Santa Marta, Lisbon, Portugal; D. Shah, Department of Medicine Specialities, University Hospital Geneva, Geneva, Switzerland; G-A. Dan, Colentina University Hospital, Bucharest, Romania; E. Serdechnaya, Northern State Medical University, Arkhangelsk, Russia; T. Potpara, Cardiology Clinic, Clinical Center of Serbia, Belgrade, Serbia; E. Diker, Başakşehir Çam and Sakura City

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Hospital, Istanbul, Turkey; G.Y.H. Lip, D. Lane; City Hospital, University of Birmingham, Birmingham, United Kingdom.

Participants: **ALBANIA** Durrës: E. Zëra, Tirana: U. Ekmekçiu, V. Paparisto, M. Tase, Tirana: H. Gjergo, J. Dragoti, A. Goda, **BELGIUM** Bastogne: M. Ciutea, N. Ahadi, Z. el Husseini, M. Raepers, Gilly: J. Leroy, P. Haushan, A. Jourdan, Haine Saint Paul: C. Lepiece, Hasselt: L. Desteghe, J. Vijgen, P. Koopman, G. Van Genechten, H. Heidbuchel, Kortrijk: T. Boussy, M. De Coninck, H. Van Eeckhoutte, N. Bouckaert, La Louviere: A. Friart, J. Boreux, C. Arend, Liege: P. Evrard, Liège: L. Stefan, E. Hoffer, J. Herzet, M. Massoz, Liège: C. Celentano, M. Sprynger, L. Pierard, Liège: P. Melon, Overpelt: B. Van Hauwaert, C. Kuppens, D. Faes, D. Van Lier, A. Van Dorpe, Waremme: A. Gerardy, Yvoir: O. Deceuninck, O. Xhaet, F. Dormal, E. Ballant, D. Blommaert, **BULGARIA** Pleven: D. Yakova, M. Hristov, T. Yncheva, N. Stancheva, S. Tisheva, Plovdiv: M. Tokmakova, F. Nikolov, D. Gencheva, Sofia: T. Shalganov, B. Kunev, M. Stoyanov, Sofia: D. Marchov, V. Gelev, V. Traykov, Varna: A. Kisheva, H. 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Kozlowski, T. Pawlowski, M. Tendera,

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Maidstone: B. Mishra, S. Ahmad, H. Randall, J. Hill, L. Reid, M. George, S. McKinley, L. Brockway, W. Milligan, Manchester: J. Sobolewska, J. Muir, L. Tuckis, L. Winstanley, P. Jacob, S. Kaye, L. Morby, Nottingham: A. Jan, T. Sewell, Poole: C. Boos, B. Wadams, C. Cope, P. Jefferey, Portsmouth: N. Andrews, A. Getty, A. Suttling, C. Turner, K. Hudson, R. Austin, S. Howe, Redhill: R. Iqbal, N. Gandhi, K. Brophy, P. Mirza, E. Willard, S. Collins, N. Ndlovu, Rhyl: E. Subkovas, V. Karthikeyan, L. Waggett, A. Wood, A. Bolger, J. Stockport, L. Evans, E. Harman, J. Starling, L. Williams, V. Saul, Salisbury: M. Sinha, L. Bell, S. Tudgay, S. Kemp, J. Brown, L. Frost, Shrewsbury: T. Ingram, A. Loughlin, C. Adams, M. Adams, F. Hurford, C. Owen, C. Miller, D. Donaldson, H. Tivenan, H. Button, South Shields: A. Nasser, O. Jhagra, B. Stidolph, C. Brown, C. Livingstone, M. Duffy, P. Madgwick, Southampton: P. Roberts, E. Greenwood, L. Fletcher, M. Beveridge, S. Earles, Taunton: D. McKenzie, D. Beacock, M. Dayer, M. Seddon, D. Greenwell, F. Luxton, F. Venn, H. Mills, J. Rewbury, K. James, K. Roberts, L. Tonks, Torquay: D. Felmeden, W. Taggu, A. Summerhayes, D. Hughes, J. Sutton, L. Felmeden, Watford: M. Khan, E. Walker, L. Norris, L. O'Donohoe, Weston-super-Mare: A. Mozid, H. Dymond, H. Lloyd-Jones, G. Saunders, D. Simmons, D. Coles, D. Cotterill, S. Beech, S. Kidd, Wolverhampton: B. Wrigley, S. Petkar, A. Smallwood, R. Jones, E. Radford, S. Milgate, S. Metherell, V. Cottam, Yeovil: C. Buckley, A. Broadley, D. Wood, J. Allison, K. Rennie, L. Balian, L. Howard, L. Pippard, S. Board, T. Pitt-Kerby.

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