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Obesity paradox on outcome in atrial fibrillation maintained even considering the prognostic influence of biomarkers: insights from the ARISTOTLE trial

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ABSTRACT

Objective We investigated the association between obesity and biomarkers indicating cardiac or renal dysfunction or inflammation and their interaction with obesity and outcomes.

Methods A total of 14 753 patients in the Apixaban for Reduction In STroke and Other ThromboembolLic Events in Atrial Fibrillation (ARISTOTLE) trial provided plasma samples at randomisation to apixaban or warfarin. Median follow-up was 1.9 years. Body Mass Index (BMI) was measured at baseline and categorised as normal, 18.5–25 kg/m^2; overweight, >25 to <30 kg/m^2; and obese, ≥30 kg/m^2. We analysed the biomarkers high-sensitivity C reactive protein (hs-CRP), interleukin 6 (IL-6), growth differentiation factor-15 (GDF-15), troponin T and N-terminal B-type natriuretic peptide (NT-pro-BNP). Outcomes included stroke/systemic embolism (SE), myocardial infarction (MI), composite (stroke/SE, MI, or all-cause mortality), all-cause and cardiac mortality, and major bleeding.

Results Compared with normal BMI, obese patients had significantly higher levels of hs-CRP and IL-6 and lower levels of GDF-15, troponin T and NT-pro-BNP. In multivariable analyses, higher compared with normal BMI was associated with a lower risk of all-cause mortality (overweight: HR 0.73 (95% CI 0.63 to 0.86); obese: 0.67 (0.56 to 0.80), p<0.0001), cardiac death (overweight: HR 0.74 (95% CI 0.60 to 0.93); obese: 0.71 (0.56 to 0.92), p=0.01) and composite endpoint (overweight: 0.80 (0.70 to 0.92); obese: 0.72 (0.62 to 0.84), p<0.0001).

Conclusions Regardless of biomarkers indicating inflammation or cardiac or renal dysfunction, obesity was independently associated with an improved survival in anticoagulated patients with AF.

Trial registration number NCT00412984.

Key questions

What is already known about this subject?

- Prior studies have shown that in atrial fibrillation (AF), indices of obesity are associated with a favourable prognosis.
- Recent data demonstrate elevated levels of biomarkers indicating cardiac or renal dysfunction or inflammatory activity is associated with worse outcome in AF.
- The relationship between these biomarkers and obesity and the interaction between obesity and outcomes is unclear.

What does this study add?

- This biomarker study within the ARISTOTLE (Apixaban for Reduction In STroke and Other Thromboembolic Events in Atrial Fibrillation) trial provides a unique insight into whether biomarkers may, in part, provide an explanation for obesity paradox.
- This was achieved by a comprehensive analysis of adiposity (Body Mass Index and waist circumference) and outcomes including biomarkers indicating cardiac or renal dysfunction or inflammation in the largest cohort to date of almost 15 000 patients with AF on anticoagulation from a prospective randomised trial.

How might this impact on clinical practice?

- In patients with AF on anticoagulation, measures of adiposity were associated with an improved survival irrespective of clinical factors and markers indicating myocardial and renal dysfunction and inflammation.
- Further research is needed to explain the 'obesity paradox'.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac rhythm disorder[1] and it is associated with significant morbidity and mortality.[2 3] Globally, the burden of AF is considerable and it is projected to rise over the next several decades.[4] Obesity is a well-established risk factor for occurrence[5–7] and persistence of AF[8 9] and itself is a growing epidemic,[10] which may explain the escalation in incident AF. Previous investigation from the Apixaban for Reduction in STroke and Other Thromboembolic Events in Atrial Fibrillation

(ARISTOTLE) trial[11] and other studies[12–17] have shown that in patients with established AF, an 'obesity paradox' where overweight status and obesity, primarily measured by Body Mass Index (BMI), is associated with a favourable prognosis. However, the underlying cause for this 'obesity paradox' is unclear.

Several randomised clinical trials have found increasing levels of biomarkers reflecting myocardial cell damage (cardiac troponin),[18 19] cardiac dysfunction (N-terminal pro-brain natriuretic peptide, NT-pro-BNP),[19 20] renal dysfunction (creatinine clearance and cystatin C)[21–23] and inflammation (C reactive protein, CRP; interleukin 6, IL-6; and growth differentiation factor-15, GDF-15)[24 25] are independently associated with worse prognosis in anticoagulated patients with AF. There is a paucity of data exploring the relationship between biomarkers, obesity and outcomes in patients with AF.

We therefore evaluated the association between BMI and biomarkers indicating cardiac and renal dysfunction and inflammation in 14 753 participants randomised to apixaban or warfarin in the biomarker cohort of the ARISTOTLE trial. We also evaluated the association between BMI and the risk of stroke or systemic embolism, myocardial infarction, all-cause and cardiac death, and major bleeding adjusted for clinical factors and biomarkers. In secondary analyses, we evaluated the relationship between abnormal waist circumference and outcomes after multivariable adjustment.

METHODS

Study population

The ARISTOTLE trial design and results have been previously published.[26 27] Briefly, this is a randomised, double-blind, double-dummy trial that enrolled 18 201 patients with AF and at least one additional risk factor for stroke (age >75 years; previous stroke, transient ischaemic attack (TIA) or systemic embolism; symptomatic heart failure within the previous 3 months or ejection fraction <0.40; diabetes; or hypertension on treatment) to apixaban versus warfarin. The primary outcome was stroke and systemic embolism. The biomarker cohort consisted of 14 980 participants, of which 14 753 participants had BMI values and who provided a plasma sample at the time of randomisation. For the present analyses, we included patients with available measurements of high-sensitivity CRP (hs-CRP) (n=14 660), IL-6 (n=14 727), GDF-15 (n=14 577), troponin T (n=14 672), NT-pro-BNP (n=14 668) and cystatin C (n=14 660).[18 20 22 24 25]

Definition of adiposity

The primary measure of adiposity was BMI assessed at baseline as weight (kg/m^2) and divided it into WHO categories of normal (18.5–25 kg/m^2), overweight (>25.0–29.9 kg/m^2) and obese (≥30 kg/m^2). Waist circumference was dichotomised at baseline as normal (men <102 cm, women <88 cm) and abnormal.

Outcomes

The outcomes for this study included stroke or systemic embolism (SE); myocardial infarction (MI); all-cause mortality; cardiac mortality; composite endpoint of stroke, SE, MI or all-cause mortality; and major bleeding defined by International Society of Thrombosis and Hemostasis criteria.[27] A blinded clinical events committee adjudicated all outcomes according to prespecified criteria.

Laboratory measurements

Study participants provided venous blood samples prior to the start of study treatment. Plasma was frozen in aliquots and stored at −70°C until analysed centrally at Uppsala Clinical Research Center, an academic platform for analyses of biomarkers at the Uppsala University Hospital, Uppsala, Sweden. Measurement of selected biomarkers have been described in detail previously.[18 20 22 24 25] Plasma concentrations of hs-CRP were analysed using a particle-enhanced immunoturbidimetric assay (Abbott, Abbott Park, Illinois, USA); hs-IL-6 analysed using an ELISA technique (R&D Systems, Minneapolis, Minnesota, USA); high-sensitivity assay was used for cardiac troponin T using the ARCHITECT i1000SR (Abbott Diagnostics); NT-pro-BNP with the Cobas Analytics e601; cystatin C with the ARCHITECT ci8200; GDF-15 with a pre-commercial assay from Roche Diagnostics. The lower limit of quantification and total coefficient of variation for each biomarker are as follows: hs-CRP (0.2 mg/L; 2.0% at 1.72 mg/L), cystatin C (0.4 mg/L; 1.09% at 0.85 mg/L), GDF-15 (400 pg/mL; 4.4% at 1500 pg/mL), IL-6 (0.04 ng/L; 11% at 1.2 ng/L), NT-pro-BNP (5 ng/L; 3% at 125 ng/L) and troponin T (13 ng/L; 3% at 27 ng/L).

Statistical analysis

Baseline characteristics were reported using median and first and third quartiles for continuous variables and frequencies and percentages for categorical variables. The characteristics were compared across categories of BMI using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables, respectively. Cox proportional-hazards models were used to estimate HRs and 95% CIs across categories of BMI (≤25 kg/m^2 as referent) and waist circumference (men <102 cm, women <88 cm, as referent), the latter also separately for men and women. The models included established risk factors (age sex, region, estimated glomerular filtration rate, smoking, systolic blood pressure, heart rate, AF type, diabetes mellitus, heart failure, previous stroke or systemic embolism/TIA, hypertension, previous MI, previous peripheral artery disease/coronary artery bypass graft/percutaneous coronary intervention, alcohol, baseline medications, prior warfarin/vitamin K antagonist treatment; for bleeding endpoints: haematocrit, chronic liver disease, history of anaemia, use of non-steroidal inflammatory agents and history of spontaneous or clinical relevant bleeding), randomised treatment and biomarkers (hs-CRP, IL-6, GDF-15, troponin T,

Table 1 Baseline characteristics according to categories of BMI for 14 753 participants in the biomarker cohort

Characteristics	BMI category ≥18.5–25 kg/m^2 (n=3294)	>25–29.9 kg/m^2 (n=5515)	≥30 kg/m^2 (n=5944)	P values*
Demographics				
Age, median (IQR), years	72.0 (66.0–78.0)	71.0 (64.0–77.0)	67.0 (61.0–73.0)	<0.0001
Female, n (%)	1309 (39.7)	1665 (30.2)	2249 (37.8)	<0.0001
Ethnicity, n (%)				<0.0001
Caucasian	2155 (65.4)	4568 (82.8)	5591 (94.1)	
Asian	1037 (31.5)	805 (14.6)	214 (3.6)	
Black	39 (1.2)	53 (1.0)	84 (1.4)	
Native Hawaiian/Other Pacific	0 (0.0)	1 (0.0)	2 (0.0)	
American Indian/Alaska Native	11 (0.3)	19 (0.3)	8 (0.1)	
Other	52 (1.6)	69 (1.3)	44 (0.7)	
Clinical				
Systolic blood pressure, median (IQR), mm Hg	130.0 (120.0–140.0)	130.0 (120.0–140.0)	131.0 (120.0–140.0)	<0.0001
Heart rate, median (IQR), bpm	75.0 (65.0–85.0)	74.0 (65.0–84.0)	76.0 (66.0–86.0)	<0.0001
History of hypertension, n (%)	2631 (79.9)	4784 (86.7)	5537 (93.2)	<0.0001
History of stroke, TIA or systemic embolism, n (%)	845 (25.7)	1078 (19.5)	925 (15.6)	<0.0001
History of myocardial infarction, n (%)	376 (11.4)	712 (12.9)	816 (13.7)	0.006
Peripheral artery disease, n (%)	166 (5.0)	257 (4.7)	301 (5.1)	0.56
Heart failure, n (%)	955 (29.0)	1643 (29.8)	1974 (33.2)	<0.0001
Diabetes mellitus, n (%)	529 (16.1)	1186 (21.5)	1952 (32.8)	<0.0001
Paroxysmal AF, n (%)	497 (15.1)	830 (15.1)	911 (15.3)	0.91
eGFR, median (IQR), mL/min/17.32	68.2 (55.0–81.6)	67.9 (55.7–80.5)	69.4 (56.3–83.3)	<0.0001
LVEF, mean (SD), %	56.0 (45.0–64.0)	56.0 (47.0–64.0)	55.0 (47.0–63.0)	0.75
Left atrial size, median (IQR), cm	4.5 (3.9–5.0)	4.6 (4.1–5.2)	4.7 (4.2–5.2)	<0.0001
Smoker, n (%)	304 (9.2)	445 (8.1)	451 (7.6)	0.02
Alcohol, per day, n (%)				<0.0001
None	2145 (65.2)	3042 (55.2)	3338 (56.2)	
<3	1072 (32.6)	2319 (42.1)	2454 (41.3)	
>3	73 (2.2)	149 (2.7)	148 (2.5)	
History of anaemia, n (%)	243 (7.4)	325 (5.9)	420 (7.1)	0.01
History of spontaneous or clinically relevant bleed, n (%)	499 (15.2)	906 (16.4)	1001 (16.8)	0.10
Baseline medication, n (%)				
Clopidogrel	74 (2.2)	98 (1.8)	85 (1.4)	0.02
Aspirin	1015 (30.8)	1700 (30.8)	1863 (31.3)	0.80
Calcium channel blocker	879 (26.7)	1653 (30.0)	1987 (33.4)	<0.0001
Beta-blocker	1856 (56.3)	3477 (63.0)	4031 (67.8)	<0.0001
ACE inhibitor/ARB	2014 (61.1)	3845 (69.7)	4597 (77.3)	<0.0001
Lipid-lowering agent	1225 (37.2)	2427 (44.0)	2947 (49.6)	<0.0001
NSAID	220 (6.7)	368 (6.7)	653 (11.0)	<0.0001
Prior vitamin K antagonist use	1574 (47.8)	2916 (53.0)	3460 (58.3)	<0.0001
Biomarker				
hs-CRP (mg/L)	1.5 (0.7–3.6)	1.9 (0.9–4.1)	2.9 (1.4–5.8)	<0.0001
IL-6 (ng/L)	2.2 (1.3–3.9)	2.2 (1.4–3.6)	2.5 (1.7–4.1)	<0.0001
GDF-15 (ng/L)	1490.5 (1058.2–2218.8)	1369.5 (970.0–2002.8)	1328.0 (946.0–1980.5)	<0.0001
Troponin T (ng/L)	11.3 (7.7–17.1)	11.1 (7.6–16.8)	10.7 (7.4–16.2)	<0.001

Continued

Table 1 Continued

Characteristics	BMI category ≥18.5–25 kg/m^2 (n=3294)	>25–29.9 kg/m^2 (n=5515)	≥30 kg/m^2 (n=5944)	P values*
NT-pro-BNP (ng/L)	879.5 (443.0–1544.5)	724.0 (378.0–1255.8)	622.5 (324.0–1070.0)	<0.0001
Cystatin C (mg/L)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.01

*P value from the χ^2 test (categorical variables) or Kruskal-Wallis test (continuous variables).
AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, Body Mass Index; GDF-15, growth differentiation factor-15; IL-6, interleukin 6; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal B-type natriuretic peptide; NSAID, non-steroidal anti-inflammatory drug; TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C reactive protein.

NT-pro-BNP and cystatin C). For waist circumference, a reduced model for stroke or systemic embolus and MI included age, sex, region, diabetes mellitus, heart failure, previous stroke or systemic embolism/TIA, hypertension, previous MI, previous peripheral artery disease/coronary artery bypass graft/percutaneous coronary intervention, prior warfarin/vitamin K antagonist treatment, randomised treatment and biomarkers. Restricted cubic splines with four knots placed at the 5th, 35th, 65th and 95th sample percentiles were used to allow for non-linear relationship between continuous variables and outcomes that included death. Splines were used in all cases when adjustment for biomarkers were performed. All analyses were performed using R, V.3.3.2. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Baseline demographics, clinical characteristics, medications and biomarkers across categories of BMI are shown in table 1. Patients with a normal BMI were older and more likely to have Asian ethnicity; have a history of stroke, TIA or systemic embolism or anaemia; and a non-drinker. Patients with a normal BMI were less likely to be prescribed an ACE inhibitor or angiotensin receptor blocker, or AV nodal blocking agent, or lipid-lowering agent, or to have prior vitamin K antagonist use compared with patients with a higher BMI.

BMI and biomarkers

With respect to biomarkers, obese patients had higher levels of hs-CRP and IL-6 and lower levels of GDF-15, troponin T and NT-pro-BNP, compared with patients with normal BMI at baseline (table 1). In multivariable analysis, hs-CRP, IL-6, troponin T and cystatin C were statistically significantly associated with higher BMI while GDF-15 and NT-pro-BNP were statistically significantly associated with lower BMI (table 2).

BMI and outcomes

In a median follow-up of 1.9 years, there were 391 stroke or systemic embolism events, 149 myocardial infarctions, 1040 all-cause mortality events, 530 cardiac deaths, 1406 composite events and 663 major bleeding events. The overall unadjusted annualised rate of efficacy and safety events was lower for patients with a higher BMI compared with those with a normal BMI (figure 1) in accordance with the corresponding results in the total ARISTOTLE cohort.[11] In multivariable analyses, adjusting for established AF risk factors, study treatment and biomarkers indicating cardiac and renal dysfunction and inflammation, higher BMI was associated with lower risk of all-cause mortality (overweight: HR 0.73 (95% CI 0.63 to 0.86); obese: HR 0.67 (95% CI 0.56 to 0.80), p<0.0001), cardiac death (overweight: HR 0.74 (95% CI 0.60 to 0.93); obese: HR 0.71 (95% CI 0.56 to 0.92), p<0.01) and composite endpoint (overweight: HR 0.80 (95% CI 0.70 to 0.92); obese: HR

Table 2 Multivariable adjusted model of biomarker effect on Body Mass Index

Biomarker	Q1	Q3	Difference	Effect	95% CI	P values
hs-CRP (mg/L), IQR	1.0	4.7	3.7	1.50	1.26 to 1.73	<0.001
IL-6 (ng/L), IQR	1.5	3.9	2.4	0.97	0.74 to 1.20	<0.001
GDF-15 (mg/L), IQR	974.0	2047.0	1073	−0.60	−8.84 to -0.36	<0.001
Troponin T (ng/L), IQR	7.5	16.6	9.1	0.31	0.07 to 0.55	0.004
NT-pro-BNP (ng/L), IQR	362.0	1241.0	879.0	−1.46	−1.68 to -1.24	<0.001
Cystatin C (mg/L), IQR	0.8	1.2	0.4	1.18	0.93 to 1.43	<0.001

Model adjusted for all variables in table 1.
GDF-15, growth differentiation factor-15; hs-CRP, high-sensitivity C reactive protein; IL-6, interleukin 6; NT-pro-BNP, N-terminal B-type natriuretic peptide.

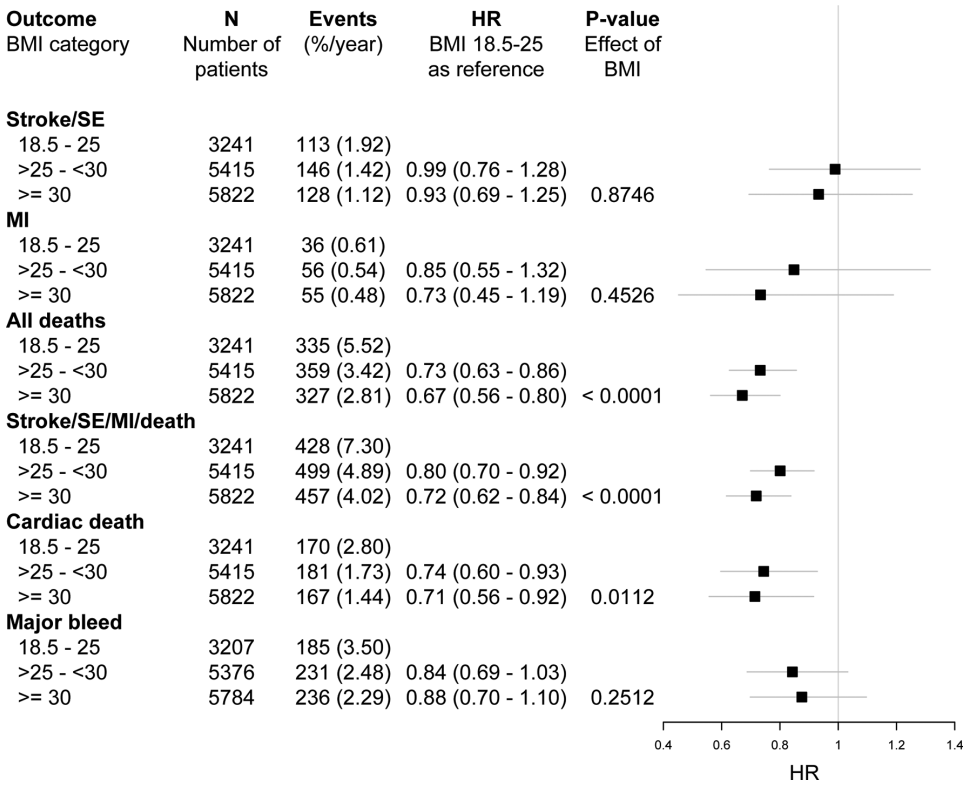

Figure 1 Multivariable-adjusted HRs and 95% CIs of outcomes according to categories of BMI adjusting for established risk factors, study treatment and cardiac, renal and inflammatory biomarkers. Multivariable models adjusted for age, sex, region, glomerular filtration rate, smoking, systolic blood pressure, heart rate, atrial fibrillation type, diabetes, heart failure, previous stroke or systemic embolism or transient ischaemic attack, hypertension, previous myocardial infarction, previous peripheral artery disease/coronary artery bypass graft/percutaneous coronary intervention, alcohol, baseline medications, prior warfarin/vitamin K antagonist treatment, randomised treatment, hs-CRP, IL-6, GDF-15, troponin T, NT-pro-BNP and cystatin C. For bleeding endpoints: haematocrit, chronic liver disease, history of anaemia, use of non-steroidal inflammatory agents and history of spontaneous or clinical relevant bleeding, randomised treatment and hs-CRP, IL-6, GDF-15, troponin T, NT-pro-BNP and cystatin C. BMI, Body Mass Index; GDF-15, growth differentiation factor-15; hs-CRP, high-sensitivity C reactive protein; IL-6, interleukin 6; MI, myocardial infarction; NT-pro-BNP, N-terminal pro-brain natriutetic peptide.

0.72 (95% CI 0.62 to 0.84), p<0.0001, figure 1), though mainly driven by the reduction in mortality as there were no associations with stroke or systemic embolism (p=0.87), MI (p=0.45) or major bleeding (p=0.25). A higher BMI was associated with lower risk of all-cause mortality, cardiac deaths and composite endpoint also in models which adjusted for biomarkers troponin T, NT-pro-BNP and cystatin C and separately for inflammatory biomarkers hs-CRP, IL-6 and GDF-15 (online supplementary material 1).

Waist circumference and outcomes

Overall, we found no statistically significant association between abnormal waist circumference and any of the outcomes except for all-cause mortality (figure 2, HR 0.87 (95% CI 0.75 to 0.99), p=0.04) after adjusting for covariates including all biomarkers. In women, an abnormal waist circumference was statistically significantly associated with a lower risk of the composite endpoint compared with normal waist circumference in multivariable analysis (HR 0.79 (95% CI 0.64 to 0.98), p=0.03; figure 3). In men, there was no statistically significant association between abnormal waist circumference and outcomes. In a separate analysis adjusting for established risk factors and hs-CRP, IL-6 and GDF-15, there was a relative risk reduction of 30% in stroke or systemic embolism (p=0.0461), 30% in all-cause mortality (p=0.01), 28% in the composite endpoint (p=0.002) and 38% in cardiac mortality (p=0.01) among women and a 16% relative risk reduction in all-cause mortality in men with abnormal waist circumference compared with normal waist circumference (online supplementary material 1). All results were attenuated after adjustment for troponin T, NT-pro-BNP and cystatin C (online supplementary material 1).

DISCUSSION

In a large cohort of patients with AF treated with oral anticoagulation therapy in the ARISTOTLE trial, overweight status and obesity were associated with lower risk of all-cause mortality, cardiac death and a composite endpoint of stroke or systemic embolism, MI and all-cause mortality even after adjusting for the levels of biomarkers indicating cardiac and renal dysfunction and inflammatory activity. There was no independent association with

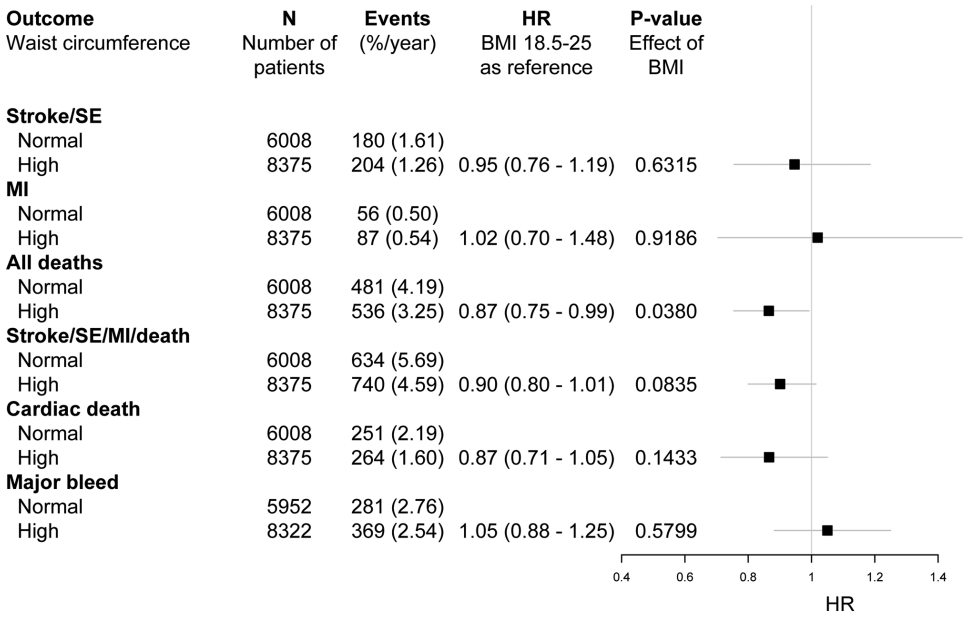

Figure 2 Multivariable-adjusted HRs and 95% CIs for outcomes for waist circumference. Waist circumference for men <102 cm and women <88 cm, as referent. Multivariable models adjusted for same covariates in figure 1 except for the outcomes of stroke or systemic embolism and myocardial infarction, for which a reduced model was used adjusting for age, region, diabetes mellitus, previous stroke or systemic embolism or transient ischaemic attack, heart failure, hypertension, previous myocardial infarction, previous peripheral artery disease/coronary artery bypass graft/percutaneous coronary intervention, prior warfarin/vitamin K agonist treatment, randomised treatment and all biomarkers. BMI, Body Mass Index; MI, myocardial infarction; SE, systemic embolism.

waist circumference and outcomes on the overall cohort except for a 13% risk reduction in all-cause mortality. However, it is noteworthy that in women, abnormal waist circumference was also associated with a 21% lower risk of the composite endpoint independent of the biomarker levels. There was no significant association between BMI or waist circumference and major bleeding in multivariable analysis adjusting for biomarker levels.

Elevated levels of inflammatory markers have been associated with initiation and persistence of AF[28–30] and found to predict cardiovascular outcomes including death in patients with AF.[20 24 31 32] Adipose tissue is a source of primary inflammatory cytokines that play a central role in obesity-induced inflammation and specific inflammatory mediators.[33 34] Prior work has found BMI is an independent predictor of increased serum levels of CRP, tumour necrosis alpha (TNF-α) and IL-6 among obese women compared with controls.[33] Importantly, a reduction of 10% in body weight was associated with relevant reductions in these inflammatory markers. Similarly, we found the highest levels of both hs-CRP and IL-6 in our obese patients with AF and the association with higher BMI remained significant in multivariable analysis. In contrast, serum levels of GDF-15, a marker of oxidative stress and inflammation and prognostic marker for death and bleeding in AF,[25] were lower in obese compared with non-obese patients. There is growing evidence from both experimental and human studies[35–37] to strongly suggest the role of GDF-15 in regulating body weight by suppressing appetite via its receptor GFRAL in the brainstem and its effects on metabolic function by improving glucose intolerance, and these may be more predominate, explaining the higher levels in our non-obese patients.

In the present analysis, the obesity paradox persisted after adjusting for all baseline characteristics, comorbidities and biomarkers. We also observed a graded reduction in all-cause mortality, cardiac death and composite endpoint from overweight to obesity. There are several explanations for this finding. In our study and other randomised clinical trials demonstrating an obesity paradox in AF,[12 13 15] age, which is an important prognostic factor, was lower in the overweight and obese patients compared with normal and is an important confounder concerning all biomarker levels. We also found lower levels of NT-pro-BNP, one of the strongest biomarkers with prognostic value in AF,[19 20] among the obese in our cohort. In obesity, lower ANP levels and production of TNF-α receptors may reduce inflammation, alter the arrhythmogenic substrate and add a protective mechanism, while an increase in plasma GDF-15 levels, as seen in our non-obese patients, has been linked to anorexia/cachexia seen in cancer and other chronic disease (ie, heart failure) and poor outcomes.[38] In addition, the use of ACE inhibitor therapy was higher among our obese patients with AF, and data suggest blockage of the renin–angiotensin system is anti-inflammatory (reducing levels of CRP and IL-6), improves endothelial function, prevents atrial fibrosis and remodelling, and reduces morbidity and mortality.[39–41] It is possible that cardiac, renal and inflammatory biomarkers have differing effects with some more pronounced than others, and this may, in part, explain the persistence of the obesity paradox.

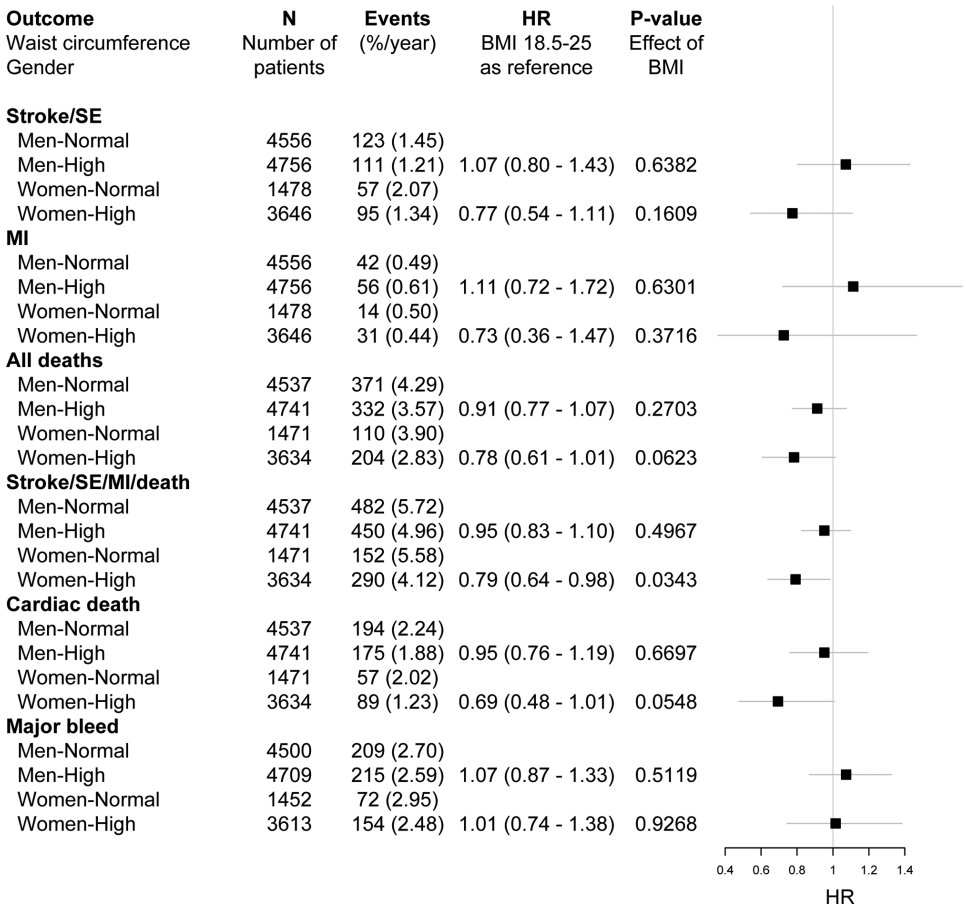

Figure 3 Multivariable-adjusted HRs and 95% CIs for outcomes for waist circumference according to sex. Waist circumference men <102 cm and women <88 cm, as referent. Multivariable models adjusted for same covariates in figure 1. BMI, Body Mass Index; MI, myocardial infarction; SE, systemic embolism.

Importantly, certain biomarkers are associated with pathological processes reflective of a variety of underlying comorbidities or conditions, and this non-specific nature may also explain why no independent effect after adjustment in relation to the obesity paradox was observed. The favourable prognosis associated with overweight and obesity in patients with AF is likely complex and multifactorial and requires further investigation.

A previous substudy of ARISTOTLE demonstrated for the first time that abnormal waist circumference is also associated with a favourable prognosis.[11] In this analysis, we found the obesity paradox, measured by waist circumference, was present in models adjusting for markers of inflammation but was no longer evident when adjusting for biomarkers indicating myocardial and renal function alone. The different prognostic value of waist circumference, as compared with BMI, may be a reflection of the different measures of adiposity. While BMI reflects total adiposity, abdominal adiposity better reflects metabolic abnormalities[42 43] that lead to the development of cardiovascular risk factors and cardiovascular disease, and adjustment of biomarkers specific to those conditions may explain the attenuated results. Additional investigations are needed to better understand differing measures of adiposity, the underlying pathophysiology and outcomes in AF treated with anticoagulation therapy.

We did demonstrate that sex differences exist with respect to waist circumference and outcomes. Although not well understood, there are data to suggest rates of accumulation of abdominal adiposity relative to concomitant losses of fat-free mass with advancing age differ among sexes, that is, mean waist circumference increases substantially more for each decade of age in women more than men.[44] In postmenopausal women, as reflected in our cohort, accumulation of visceral fat is markedly accelerated while lean body mass is less.[45 46] This increased abdominal adiposity potentially leads to greater metabolic reserve and ability to deal with stress compared with lean individuals resulting in a protective mechanism.[47 48]

This is a prospective study with the largest cohort of patients with AF and biomarkers, various measures of adiposity and strictly adjudicated outcomes. There are limitations that warrant discussion. First, baseline BMI and waist circumference were used and therefore the associations between long-term changes in adiposity measures on outcomes were not assessed. Second, it is possible that other unmeasured biomarkers may

explain the 'obesity paradox'. Adipocytes are known to synthesise specific inflammatory mediators such as adiponectin, leptin and resistin, which act on a variety of tissues to influence physiological processes.[49] Adiponectin is a plasma protein known to have protective effects against obesity-related inflammatory conditions[49] while abnormal levels of leptin has been associated with low body weight,[50] which may contribute to poor nutritional status[51] and may lead to intolerance of metabolic stress[48] and poor outcomes.[52] Evaluation of these peptide hormones and the interplay between other inflammatory and cardiovascular biomarkers for measures of adiposity are needed. Third, this is a clinical trial population, which may differ than a general AF population with relation to obesity and consequently confer varying risk on outcomes even after adjusting for various biomarkers. Fourth, there may be presence of residual confounding after adjusting for a range of confounding variable in our models.

In summary, this large prospective cohort of patients with anticoagulated AF supports that adiposity is associated with an improved survival irrespective of clinical factors and markers indicating myocardial and renal dysfunction and inflammation. Further research is needed to better understand the obesity paradox.

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REFERENCES

1. Go AS, Hylek EM, Phillips KA, *et al*. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial fibrillation (ATRIA) study. *JAMA* 2001;285:2370–5.
2. Conen D, Chae CU, Glynn RJ, *et al*. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. *JAMA* 2011;305:2080–7.
3. Lubitz SA, Moser C, Sullivan L, *et al*. Atrial fibrillation patterns and risks of subsequent stroke, heart failure, or death in the community. *J Am Heart Assoc* 2013;2:e000126.
4. Miyasaka Y, Barnes ME, Gersh BJ, *et al*. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119–25.
5. Tedrow UB, Conen D, Ridker PM, *et al*. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). *J Am Coll Cardiol* 2010;55:2319–27.
6. Wang TJ, Parise H, Levy D, *et al*. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;292:2471–7.
7. Wanahita N, Messerli FH, Bangalore S, *et al*. Atrial fibrillation and obesity—results of a meta-analysis. *Am Heart J* 2008;155:310–5.
8. Tsang TS, Barnes ME, Miyasaka Y, *et al*. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. *Eur Heart J* 2008;29:2227–33.
9. Sandhu RK, Conen D, Tedrow UB, *et al*. Predisposing factors associated with development of persistent compared with paroxysmal atrial fibrillation. *J Am Heart Assoc* 2014;3:e000916.
10. World Health Organization. *Obesity and overweight fact sheet 311*, 2015.
11. Sandhu RK, Ezekowitz J, Andersson U, *et al*. 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;37:2869–78.
12. Ardestani A, Hoffman HJ, Cooper HA. Obesity and outcomes among patients with established atrial fibrillation. *Am J Cardiol* 2010;106:369–73.
13. Badheka AO, Rathod A, Kizilbash MA, *et al*. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. *Am J Med* 2010;123:646–51.
14. Senoo K, Lip GY. Body mass index and adverse outcomes in elderly patients with atrial fibrillation: The AMADEUS Trial. *Stroke* 2016;47:523–6.
15. Proietti M, Lane DA, Lip GY. Relation of nonvalvular atrial fibrillation to body mass index (from the SPORTIF Trials). *Am J Cardiol* 2016;118:72–8.
16. Overvad TF, Rasmussen LH, Skjøth F, *et al*. Body mass index and adverse events in patients with incident atrial fibrillation. *Am J Med* 2013;126:e9–17.
17. Proietti M, Guiducci E, Cheli P, *et al*. 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;48:857–66.
18. Hijazi Z, Wallentin L, Siegbahn A, *et al*. High-sensitivity troponin T and risk stratification in patients with atrial fibrillation during treatment with apixaban or warfarin. *J Am Coll Cardiol* 2014;63:52–61.
19. Hijazi Z, Oldgren J, Andersson U, *et al*. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation* 2012;125:1605–16.
20. Hijazi Z, Wallentin L, Siegbahn A, *et al*. N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation). *J Am Coll Cardiol* 2013;61:2274–84.
21. Hijazi Z, Hohnloser SH, Oldgren J, *et al*. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation* 2014;129:961–70.
22. Hohnloser SH, Hijazi Z, Thomas L, *et al*. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J* 2012;33:2821–30.
23. Piccini JP, Stevens SR, Chang Y, *et al*. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation* 2013;127:224–32.
24. Hijazi Z, Aulin J, Andersson U, *et al*. Biomarkers of inflammation and risk of cardiovascular events in anticoagulated patients with atrial fibrillation. *Heart* 2016;102:508–17.
25. Wallentin L, Hijazi Z, Andersson U, *et al*. Growth differentiation factor 15, a marker of oxidative stress and inflammation, for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation* 2014;130:1847–58.
26. Granger CB, Alexander JH, McMurray JJ, *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
27. Lopes RD, Alexander JH, Al-Khatib SM, *et al*. Apixaban for reduction in stroke and other ThromboembоLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J* 2010;159:331–9.
28. Bruins P, te Velthuis H, Yazdanbakhsh AP, *et al*. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation* 1997;96:3542–8.
29. Chung MK, Martin DO, Sprecher D, *et al*. C-Reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001;104:2886–91.
30. Gedikli O, Dogan A, Altuntas I, *et al*. Inflammatory markers according to types of atrial fibrillation. *Int J Cardiol* 2007;120:193–7.
31. Hermida J, Lopez FL, Montes R, *et al*. Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In Communities (ARIC) Study). *Am J Cardiol* 2012;109:95–9.
32. Conway DS, Buggins P, Hughes E, *et al*. Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation. *Am Heart J* 2004;148:462–6.
33. Marfella R, Esposito K, Siniscalchi M, *et al*. Effect of weight loss on cardiac synchronization and proinflammatory cytokines in premenopausal obese women. *Diabetes Care* 2004;27:47–52.
34. Ziccardi P, Nappo F, Giugliano G, *et al*. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* 2002;105:804–9.
35. Tran T, Yang J, Gardner J, *et al*. GDF15 deficiency promotes high fat diet-induced obesity in mice. *PLoS One* 2018;13:e0201584.
36. Yang L, Chang CC, Sun Z, *et al*. GFRAL is the receptor for GDF15 and is required for the anti-obesity effects of the ligand. *Nat Med* 2017;23:1158–66.
37. Vila G, Riedl M, Anderwald C, *et al*. The relationship between insulin resistance and the cardiovascular biomarker growth differentiation factor-15 in obese patients. *Clin Chem* 2011;57:309–16.
38. Mullican SE, Rangwala SM. Uniting GDF15 and GFRAL: therapeutic opportunities in obesity and beyond. *Trends Endocrinol Metab* 2018;29:560–70.
39. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, *et al*. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145–53.
40. SOLVD Investigators, Yusuf S, Pitt B, *et al*. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302.
41. van Vark LC, Bertrand M, Akkerhuis KM, *et al*. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158,998 patients. *Eur Heart J* 2012;33:2088–97.
42. Seidell JC. Waist circumference and waist/hip ratio in relation to all-cause mortality, cancer and sleep apnea. *Eur J Clin Nutr* 2010;64:35–41.
43. Yusuf S, Hawken S, Ounpuu S, *et al*. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case–control study. *Lancet* 2005;366:1640–9.
44. Freiberg MS, Pencina MJ, D'Agostino RB, *et al*. BMI vs. waist circumference for identifying vascular risk. *Obesity* 2008;16:463–9.
45. Kotani K, Tokunaga K, Fujioka S, *et al*. Sexual dimorphism of age-related changes in whole-body fat distribution in the obese. *Int J Obes Relat Metab Disord* 1994;18:207–2.
46. Trémollieres FA, Pouilles JM, Ribot CA. Relative influence of age and menopause on total and regional body composition changes in postmenopausal women. *Am J Obstet Gynecol* 1996;175:1594–600.
47. Romero-Corral A, Montori VM, Somers VK, *et al*. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;368:666–78.
48. Lavie CJ, Alpert MA, Arena R, *et al*. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail* 2013;1:93–102.
49. Scridon A, Dobreanu D, Chevalier P, *et al*. Inflammation, a link between obesity and atrial fibrillation. *Inflamm Res* 2015;64:383–93.
50. Haynes WG, Morgan DA, Walsh SA, *et al*. Receptor-mediated regional sympathetic nerve activation by leptin. *J Clin Invest* 1997;100:270–8.
51. Franceschini R, Tenconi GL, Zoppoli F, *et al*. Endocrine abnormalities and outcome of ischaemic stroke. *Biomed Pharmacother* 2001;55:458–65.
52. Simoons ML, Bonneux L, Obesity BL. Obesity, cardiology, and beyond. *J Am Coll Cardiol* 2008;52:986–7.