Is There an Obesity Paradox for Outcomes in Atrial Fibrillation?

A Systematic Review and Meta-Analysis of Non–Vitamin K Antagonist Oral Anticoagulant Trials

Marco Proietti, MD; Elisa Guiducci, MD; Paola Cheli, MD; Gregory Y.H. Lip, MD

Background and Purpose—Obesity is a risk factor for all-cause and cardiovascular death but, despite this, an inverse relationship between overweight or obesity and a better cardiovascular prognosis in long-term follow-up studies has been observed; this phenomenon, described as obesity paradox, has also been found evident in atrial fibrillation cohorts.

Methods—We performed a systematic review on the relationship between body mass index and major adverse outcomes in atrial fibrillation patients. Moreover, we provided a meta-analysis of non–vitamin K antagonist oral anticoagulants (NOACs) trials.

Results—An obesity paradox was found for cardiovascular death and all-cause death in the subgroup analyses of randomized trial cohorts; however, observational studies fail to show this relationship. From the meta-analysis of NOAC trials, a significant obesity paradox was found, with both overweight and obese patients reporting a lower risk for stroke/systemic embolic event (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.66–0.84 and OR, 0.62; 95% CI, 0.54–0.70, respectively). For major bleeding, only obese patients were at lower risk compared with normal weight patients (OR, 0.84; 95% CI, 0.72–0.98). A significant treatment effect of NOACs was found in normal weight patients, both for stroke/systemic embolic event (OR, 0.66; 95% CI, 0.56–0.78) and for major bleeding (OR, 0.72; 95% CI, 0.54–0.95). Major bleeding risk was lower in overweight patients treated with NOACs (OR, 0.84; 95% CI, 0.71–1.00).

Conclusions—There may be an obesity paradox in atrial fibrillation patients, particularly for all-cause and cardiovascular death outcomes. An obesity paradox was also evident for stroke/systemic embolic event outcome in NOAC trials, with a treatment effect favoring NOACs over warfarin for both efficacy and safety that was significant only for normal weight patients. **(*Stroke*. 2017;48:857-866. DOI: 10.1161/STROKEAHA.116.015984.)**

Key Words: anticoagulants ■ atrial fibrillation ■ body weight ■ heart failure ■ obesity

In the general population, the presence of obesity represents one of the most important risk factors for cardiovascular disease, cardiovascular death, and all-cause death.[1] Indeed, body mass index (BMI) has a continuous positive relationship with CVD risk.[2] All major international guidelines on CVD prevention recommend to attainment and maintenance of an healthy weight to achieve a reduction in cardiovascular risk and incident cardiovascular events.[2,3]

Despite this, an inverse relationship between overweight or obesity and a better cardiovascular prognosis in long-term follow-up studies has been observed, a phenomenon described as an obesity paradox.[4,5] Several studies have found an obesity paradox is evident in patients with established cardiovascular disease, including hypertension, coronary heart disease, and chronic heart failure.[6] An obesity paradox may also be evident in primary prevention patients.[7]

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia, and the relationship between obesity and AF is well established. Several studies have reported epidemiological, clinical, and mechanistic associations, clearly establishing a pathophysiological cause–effect relationship between obesity and incident AF.[8] Interventions aimed at weight reduction are associated with a reduction in the risk of developing AF.[9,10] In patients with established AF, an obesity paradox is also evident for the risk of developing major adverse events,[11] even if this risk seems to be mitigated by a good-quality anticoagulation control.[12]

To study this, we performed a systematic review and meta-analysis with several objectives, as follows: (1) to provide a comprehensive report of all available evidence on the relationship between overweight and obesity in AF patients; (2) to perform a comparative analysis of observational studies and

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subgroup analyses from randomized clinical trials (RCTs); and (3) to conduct a meta-analysis of available data on the relationship of BMI to stroke/systemic embolic event (SEE) and major bleeding in the phase III non–vitamin K antagonist oral anticoagulant (NOAC) trials of stroke prevention in AF.

Methods

All prospective studies, both RCTs and observational, reporting data about AF and BMI categories were considered eligible for the systematic review. A comprehensive literature search was performed using PubMed and Scopus databases, up to June 30, 2016.

Data for meta-analysis were retrieved from original phase III trials or from regulatory documentation. Data extraction and bias assessment were performed independently by 2 coauthors, with discrepancies resolved by collegial discussion. All statistical analyses were undertaken using Review Manager (RevMan) version 5.3 (The Cochrane Collaboration 2014; Nordic Cochrane Center Copenhagen, Denmark). Full details of the literature search strategy, study selection criteria, quality assessment, and statistical analysis have been reported in the Methods section in the online-only Data Supplement. This work has been performed according to PRISMA guidelines (http://www.prisma-statement.org; Table I in the online-only Data Supplement).

Results

Systematic Review

On the basis of our literature search (Figure 1), 13 studies fulfilled our criteria, with details summarized in Table. Five were subgroup analyses of previously published RCTs,[11–15] whereas the other 8 were observational studies.[16–23] One study included AF patients who underwent an ablation procedure for rhythm control strategy.[21] Four observational studies were based on Asian populations.[17–19,23] In 12 out of 13 studies, the mean age progressively decreased with higher BMI categories, with the study by Overvad et al[16] being the exception (Table).

In 2016 alone, 6 other studies were published examining the relationship of BMI with outcomes in AF. Three were observational studies,[20–22] whereas the others were RCTs focused on comparisons between vitamin K antagonist and alternative anticoagulants.[12,14,15]

RCT Cohorts

Two separate studies reported subgroup analysis from the AFFIRM study (Atrial Fibrillation Follow-up Investigation of Rhythm Management). The first by Ardestani et al[13] was focused on the relationship between BMI and mortality. Rates of both all-cause and cardiovascular death were higher in patients with normal weight (5.8 and 3.1 per 100 person-years, respectively) compared with overweight (3.9 and 1.5 per 100 person-years, respectively) and obese (1.5 and 2.1 per 100 person-years, respectively) patients; however, no differences were noted in the rate of stroke.[13] A multivariate Cox regression analysis found that the relationship between both overweight and obese BMI categories with all-cause death was nonsignificant, whereas only overweight class remained significantly inversely associated with cardiovascular death (Table). Conversely, Badheka et al[11] showed a significant inverse relationship of both all-cause and cardiovascular death with overweight and obese categories, using a Cox regression analysis that was restricted to the variables that were significantly different at baseline.[11] Moreover, a combined end point

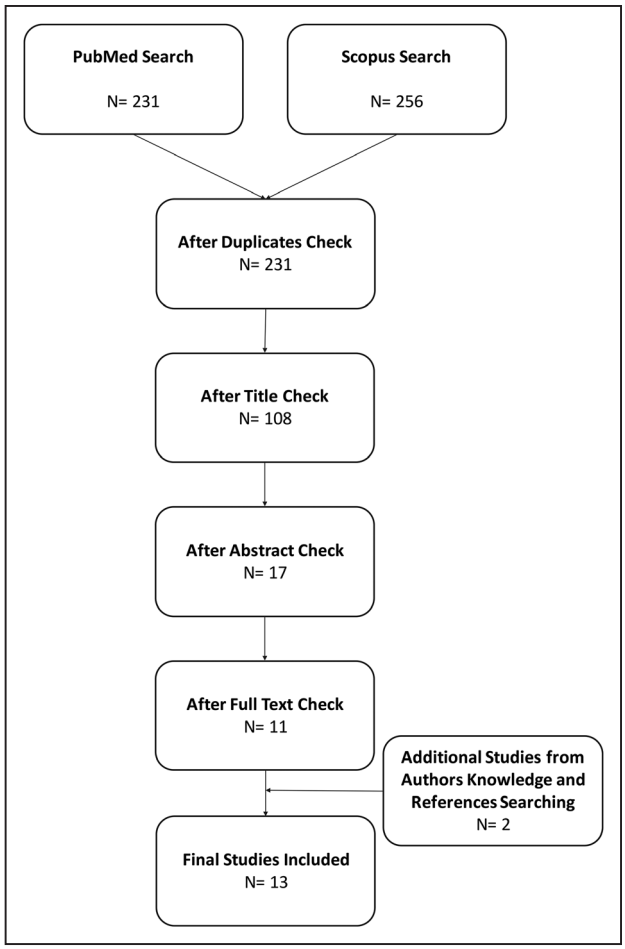

Figure 1. Systematic review studies selection.

(all-cause death, ventricular tachycardia, ventricular fibrillation, cardiac arrest, ischemic stroke, major bleeding, systemic embolism, pulmonary embolism, and myocardial infarction) was inversely associated with both overweight (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.59–0.92) and obese (HR, 0.63; 95% CI, 0.49–0.82) categories.[11]

Three other RCTs found a significant inverse association between BMI classes and outcomes. In the subgroup of patients with optimal anticoagulation control (TTR>70%), Kaplan-Meier analysis suggested a lower risk for overweight and obese AF patients for all-cause death and the composite outcome, but no association was found between overweight and obese categories after multivariate adjustment.[12] A post hoc analysis coming from ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) confirmed the inverse association between overweight and obese categories with all-cause death and a composite outcome (both $P<0.0001$), but no influence was found for stroke/systemic embolism and major bleeding outcomes ($P=0.18$ and $P=0.11$, respectively).[15]

Observational Studies

An ancillary analysis from the Danish Diet, Cancer and Health study found no relationship between the BMI categories and the occurrence of ischemic stroke/systemic embolism event both at short- and at long-term follow-up; however, after 4.9

Table. Studies Investigating the Relationship Between Atrial Fibrillation and Body Mass Index in Determining Major Adverse Outcomes

Study	Year	n	BMI Classes	Mean Age, y	Follow-Up	Outcomes*
Subgroup analyses of RCTs						
Ardestani et al[13]	2010	2492	Normal weight: 637	72.4	3 y (mean)	Cardiovascular death
			Overweight: 965	70.7		Overweight: HR, 0.47; 95% CI, 0.29–0.76; *P*=0.002
			Obese: 890	66.4		Obese: HR, 0.69; 95% CI, 0.42–1.14; *P*=0.15
						All-cause death†
						Overweight: HR, 0.74; 95% CI, 0.53–1.03; *P*=0.07
						Obese: HR, 0.82; 95% CI, 0.57–1.18; *P*=0.3
Badheka et al[11]	2010	2492	Normal weight: 637	72.4	3 y (mean)	Cardiovascular death
			Overweight: 965	70.7		Overweight: HR, 0.38; 95% CI, 0.25–0.58; *P*<0.0001
			Obese: 890	66.4		Obese: HR, 0.65; 95% CI, 0.51–0.83; *P*=0.0005
						All-cause death
						Overweight: HR, 0.66; 95% CI, 0.48–0.92; *P*=0.01
						Obese: HR, 0.58; 95% CI, 0.42–0.80; *P*=0.0009
						Combined end point†‡
						Overweight: HR, 0.73; 95% CI, 0.59–0.92; *P*=0.007
						Obese: HR, 0.63; 95% CI, 0.49–0.82; *P*=0.0004
Senoo et al[14]	2016	1588	Normal weight: 515	79.7	NA	Stroke/SE/cardiovascular death†
			Overweight: 711	79.1		Obese: HR, 0.29; 95% CI, 0.11–0.77; *P*=0.01
			Obese: 362	78.6		
Proietti et al[12]	2016	3651	Normal weight: 874	76	567 d	Stroke†
			Overweight: 1446	73	(median)	Overweight: HR, 0.61; 95% CI, 0.37–0.99
			Obese: 1310	68		Obese: HR, 0.47; 95% CI, 0.27–0.81
				(median)		Stroke/all-cause death
						Overweight: HR, 0.69; 95% CI, 0.52–0.92
						Obese: HR, 0.59; 95% CI, 0.42–0.82
Sandhu et al[15]	2016	17913	Normal weight: 4052	71.3	1.8 y (median)	Stroke/SE (*P*=0.18)†§
			Overweight: 6702	70.1		Overweight: HR, 0.86; 95% CI, 0.68–1.08
			Obese: 7159	66.8		Obese: HR, 0.79; 95% CI, 0.61–1.02
						Major bleeding (*P*=0.11)§
						Overweight: HR, 0.82; 95% CI, 0.68–0.99
						Obese: HR, 0.91; 95% CI, 0.74–1.10
						All-cause death *P*≤0.0001§
						Overweight: HR, 0.67; 95% CI, 0.59–0.78
						Obese: HR, 0.63; 95% CI, 0.54–0.74
						Stroke/SE/MI/all-cause death *P*≤0.0001§
						Overweight: HR, 0.74; 95% CI, 0.65–0.84
						Obese: HR, 0.68; 95% CI, 0.60–0.78
Observational studies						
Overvad et al[16]	2013	3135	Normal weight: 954	67.2	4.9 y (median)	Ischemic stroke/SE
			Overweight: 141	67.0		Overweight: HR, 1.14; 95% CI, 0.83–1.57; *P*=NS
			Obese: 767	66.9		Obese: HR, 0.98; 95% CI, 0.67–1.42; *P*=NS

(*Continued*)

Table. Continued

Study	Year	n	BMI Classes	Mean Age, y	Follow-Up	Outcomes*
Overvad et al[16] Continued						All-cause death
						Overweight: HR, 1.31; 95% CI, 1.07–1.59; *P*<0.05
						Obese: HR, 1.41; 95% CI, 1.13–1.75; *P*<0.05
						Ischemic stroke/SE/all-cause death†
						Overweight: HR, 1.31; 95% CI, 1.10–1.56; *P*<0.05
						Obese: HR, 1.36; 95% CI, 1.11–1.65; *P*<0.05
Wang et al[17]	2014	2016	Underweight: 164	70	12 mo (mean)	Stroke (vs overweight)
			Normal weight: 984	69		Underweight: HR, 0.88; 95% CI, 0.4–1.73; *P*=0.709
			Overweight: 651	68		Normal weight: HR, 0.85; 95% CI, 0.59–1.23; *P*=0.387
			Obese: 217	66		Obese: HR, 0.85; 95% CI, 0.47–1.51; *P*=0.568
						Major bleeding (vs overweight)
						Underweight: HR, 0.65; 95% CI, 0.14–3.02; *P*=0.580
						Normal weight: HR, 0.74; 95% CI, 0.30–1.80; *P*=0.500
						Obese: HR, 0.98; 95% CI, 0.27–3.57; *P*=0.971
						Cardiovascular death (vs overweight)
						Underweight: HR, 2.01; 95% CI, 1.76–3.43; *P*=0.011
						Normal weight: HR, 1.53; 95% CI, 1.03–2.28; *P*=0.037
						Obese: HR, 1.28; 95% CI, 0.68–2.42; *P*=0.446
						All-cause death (vs overweight)†
						Underweight: HR, 1.57; 95% CI, 1.02–2.42; *P*=0.041
						Normal weight: HR, 1.53; 95% CI, 1.13–2.03; *P*=0.005
						Obese: HR, 1.03; 95% CI, 0.61–1.75; *P*=0.909
						Combined end point (vs overweight)‖
						Underweight: HR, 1.02; 95% CI, 0.71–1.48; *P*=0.899
						Normal weight: HR, 1.14; 95% CI, 0.91–1.44; *P*=0.247
						Obese: HR, 1.04; 95% CI, 0.72–1.52; *P*=0.824
Yanagisawa et al[18]	2015	413	Underweight: 58	79.5	19 mo (mean)	Major adverse events†¶
			Normal weight: 256	77.6		Underweight: HR, 2.45; 95% CI, 1.25–4.78; *P*=0.009
			Overweight/obese: 99	75.9		Overweight/obese: HR, 0.34; 95% CI, 0.13–0.89; *P*=0.029
						All-cause death
						Underweight: HR, 2.91; 95% CI, 1.12–7.60; *P*=0.029
						Overweight/obese: HR, 0.21; 95% CI, 0.27–1.64; *P*=0.137
Wang et al[19]	2015	1286	Underweight: 386	82.08	2.1 y (median)	Ischemic stroke†
			Normal weight: 3979	76.59		Underweight: HR, 1.29; 95% CI, 0.40–4.20; *P*=0.668
			Overweight: 1739	72.15		Overweight: HR, 1.82; 95% CI, 1.16–2.84; *P*=0.009
			Obese: 275	67.92		Obese: HR, 1.02; 95% CI, 0.31–3.34; *P*=0.969
						Thromboembolism
						Underweight: HR, 1.01; 95% CI, 0.13–7.65; *P*=0.996
						Overweight: HR, 0.81; 95% CI, 0.37–1.78; *P*=0.594
						Obese: HR, 4.83; 95% CI, 1.75–13.36; *P*=0.002

(*Continued*)

Table. Continued

Study	Year	n	BMI Classes	Mean Age, y	Follow-Up	Outcomes*
Wang et al[19] Continued						Cardiovascular death
						Underweight: HR, 1.55; 95% CI, 0.47–5.10; *P*=0.336
						Overweight: HR, 0.54; 95% CI, 0.26–1.12; *P*=0.098
						Obese: HR, 0.66; 95% CI, 0.15–2.90; *P*=0.582
						All-cause death
						Underweight: HR, 2.01; 95% CI, 1.12–3.60; *P*=0.019
						Overweight: HR, 0.68; 95% CI, 0.47–0.99; *P*=0.044
						Obese: HR, 0.51; 95% CI, 0.19–1.39; *P*=0.189
Kwon et al[20]	2016	ARIC cohort: 332	Normal weight: 57	NA	6.6 y (median)	Ischemic stroke/cardiovascular death†
			Overweight: 122	NA		Overweight: HR, 0.97; 95% CI, 0.71–1.33; *P*=NS
			Obese: 153		4.4 y (median)	Obese: HR, 0.96; 95% CI, 0.69–1.32; *P*=NS
		CHS cohort: 335	Normal weight: 125			Ischemic stroke/cardiovascular death†
			Overweight: 136			Overweight: HR, 0.83; 95% CI, 0.64–1.06; *P*=NS
			Obese: 63			Obese: HR, 1.02; 95% CI, 0.74–1.41; *P*=NS
Bunch et al[21]	2016	1558	BMI ≤20 kg/m^2: 30	69.4	3 y	Log-rank analysis showed that the lowest and the highest BMI groups had the higher risk for †composite outcome#, but this difference did not reach statistical significance (*P*=0.36)
			BMI 20–25 kg/m^2: 296	68.7		
			BMI 26–30 kg/m^2: 541	66.6		
			BMI >30 kg/m^2: 691	63.6		
Pandey et al[22]	2016	9606	Normal weight: 2076	80	2 y	Stroke/TIA/non-CNS embolism (*P*=0.78)§
			Overweight: 3164	77		Overweight: HR, 0.92; 95% CI, 0.68–1.24
			Obese class I: 2173	73		Obese class I: HR, 0.94; 95% CI, 0.63–1.40
			Obese class II: 1158	70		Obese class II: HR, 0.73; 95% CI, 0.40–1.31
			Obese class III: 942	67		Obese class III: HR, 1.00; 95% CI, 0.48–2.07
				(median)		All-cause first hospitalization (*P*=0.39)§
						Overweight: HR, 0.97; 95% CI, 0.88–1.07
						Obese class I: HR, 1.04; 95% CI, 0.91–1.19
						Obese class II: HR, 0.98; 95% CI, 0.81–1.18
						Obese class III: HR, 0.97; 95% CI, 0.74–1.28
						All-cause death (*P*=0.0002)†§
						Overweight: HR, 0.81; 95% CI, 0.70–0.95
						Obese class I: HR, 0.65; 95% CI, 0.54–0.78
						Obese class II: HR, 0.85; 95% CI, 0.68–1.06
						Obese class III: HR, 0.73; 95% CI, 0.56–0.97
Inoue et al[23]	2016	6379	Underweight: 386	75	2 y	Thromboembolism†
			Normal weight: 3979	70		Underweight: HR, 1.22; 95% CI, 0.63–2.38; *P*=0.561
			Overweight: 1739	68		Overweight: HR, 0.94; 95% CI, 0.60–1.46; *P*=0.770
			Obese: 275	65		Obese: HR, 0.71; 95% CI, 0.22–2.27; *P*=0.563

(*Continued*)

Table. Continued

Study	Year	n	BMI Classes	Mean Age, y	Follow-Up	Outcomes*
Inoue et al[23] Continued						Major bleeding
						Underweight: HR, 1.71; 95% CI, 0.96–3.05; *P*=0.069
						Overweight: HR, 0.74; 95% CI, 0.47–1.16; *P*=0.192
						Obese: HR, 0.87; 95% CI, 0.35–2.19; *P*=0.771
						Cardiovascular death
						Underweight: HR, 2.91; 95% CI, 1.47–5.75; *P*=0.002
						Overweight: HR, 1.16; 95% CI, 0.58–2.30; *P*=0.680
						Obese: HR, 1.83; 95% CI, 0.54–6.20; *P*=0.332
						All-cause death
						Underweight: HR, 2.40; 95% CI, 1.59–3.63; *P*<0.001
						Overweight: HR, 0.60; 95% CI, 0.37–0.95; *P*=0.031
						Obese: HR, 1.70; 95% CI, 0.84–3.44; *P*=0.137

ACS indicates acute coronary syndrome; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CHS, Cardiovascular Health Study; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; MI, myocardial infarction; NA, not applicable; NS, not significant; RCT, randomized controlled trial; SE, systemic embolism; and TIA, transient ischemic attack.

*HR are expressed with normal weight as reference category, except where explicitly reported.

†Primary study outcome(s).

‡All-cause death, ventricular tachycardia, ventricular fibrillation, cardiac arrest, ischemic stroke, major bleeding, systemic embolism, pulmonary embolism, and myocardial infarction.

§Effect of BMI category.

‖All-cause death, cardiovascular death, stroke, non-CNS embolism, and major bleeding.

¶All-cause death, stroke/TIA, admission for heart failure, and acute coronary syndrome.

#All-cause death, stroke/TIA, and admission for heart failure.

years of follow-up, both overweight and obese categories were positively associated with the occurrence of all-cause death (HR, 1.31; 95% CI, 1.07–1.59 and HR, 1.41; 95% CI, 1.13–1.75, respectively) and the composite outcome of ischemic stroke/systemic embolism/all-cause death (HR, 1.31; 95% CI, 1.10–1.56 and HR, 1.36; 95% CI, 1.11–1.65, respectively) after adjustment for the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, vascular disease, age 65–74, sex category).[16]

The study by Bunch et al[21] focused on postablation follow-up, where higher crude event rates were reported in normal weight patients, although after adjustments these differences were no longer evident. Another study, focused on the association of modifiable cardiovascular risk factors and outcomes in incident AF patients from the ARIC study (Atherosclerosis Risk in Communities) and CHS (Cardiovascular Health Study), found that no significant differences were found in event rates for a composite outcome of ischemic stroke and cardiovascular death between normal weight patients and overweight or obese subjects.[20] Multivariate analysis confirmed no significant association of both overweight and obesity with outcomes.[20] A subgroup analysis for the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation reported that a significant inverse association was evident only for all-cause death.[22]

Asian Observational Cohorts

One large observational study from a Chinese cohort found that both underweight and normal weight were significantly associated with an increased risk for both all-cause (HR, 1.57; 95% CI, 1.02–2.42 and HR, 1.53; 95% CI, 1.13–2.03, respectively) and cardiovascular death (HR, 2.01; 95% CI, 1.76–3.43 and HR, 1.53; 95% CI, 1.03–2.28, respectively) when compared with overweight patients.[17] Despite this, no influence of BMI categories was reported for the occurrence of stroke, major bleeding, and a composite end point of several clinically relevant events.[17] Similar findings were reported in another single-center study of 1286 Chinese AF patients, where overweight patients were found to have a lower risk for all-cause death (HR, 0.68; 95% CI, 0.47–0.99) and a higher risk for underweight patients (HR, 2.01; 95% CI, 1.12–3.60).[19] A higher risk for ischemic stroke in overweight patients was found, even after multivariate adjustment.[19]

Another Japanese elderly cohort showed that being overweight resulted in a higher risk of death, but no influence was found between all-cause death and overweight/obese category.[18] However, there was an inverse association with the combined end point of all-cause death, stroke/transient ischemic attack, heart failure admission, and acute coronary syndrome (HR, 0.39; 95% CI, 0.13–0.89; *P*=0.009).[18] In this study, underweight patients were at higher risk for both major adverse events and all-cause death.[18] In a subgroup analysis from the Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) registry, underweight patients were at higher risk for both cardiovascular death (HR, 2.91; 95% CI, 1.47–5.75; *P*=0.002) and all-cause death (HR, 2.40; 95% CI, 1.59–3.63; *P*<0.001), whereas overweight patients had lower risk for all-cause death (HR, 0.60; 95% CI, 0.37–0.95).[23] No significant association was found for the obese patients nor any influence of body weight in determining thromboembolism and major bleeding.[23]

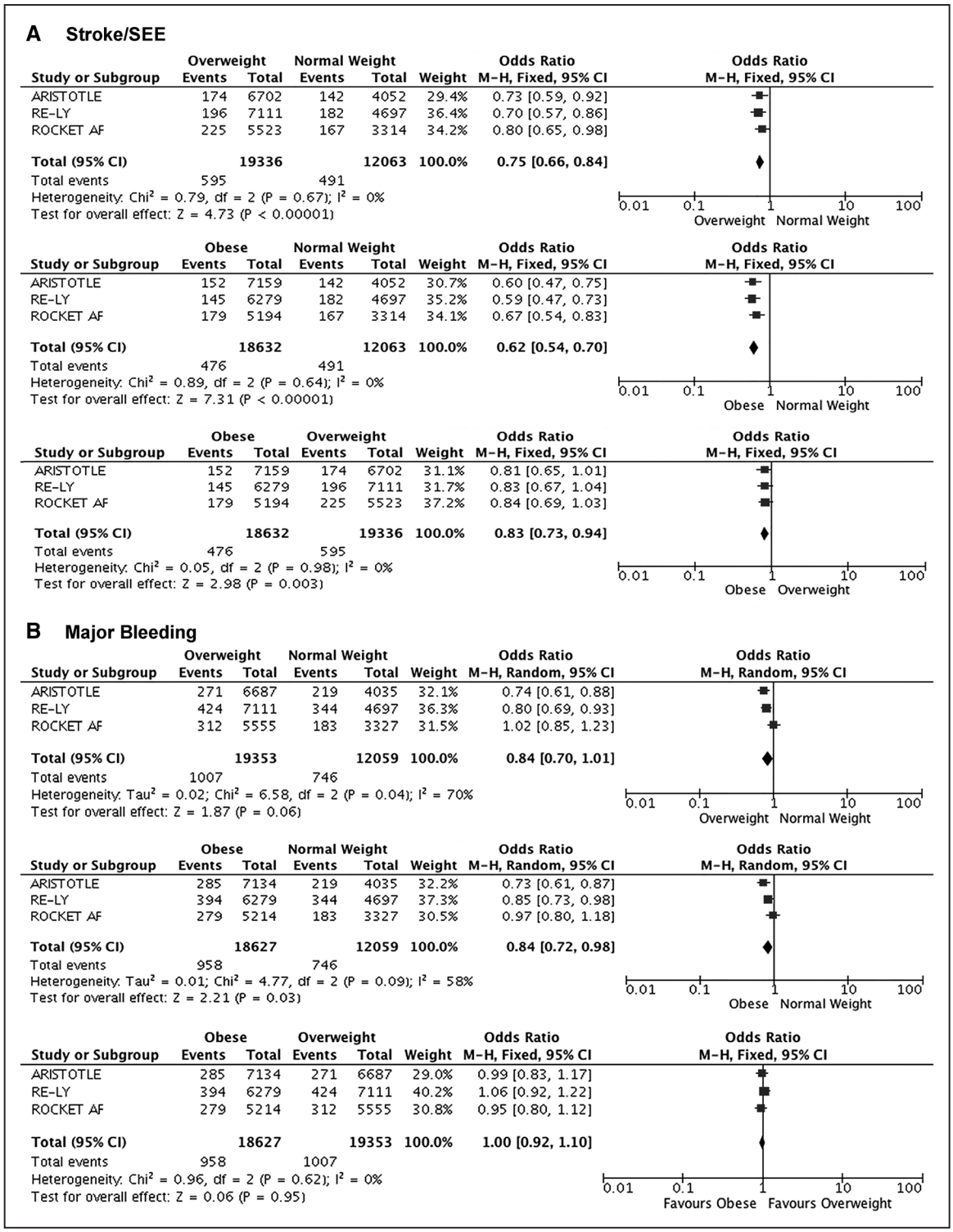

Figure 2. Body mass index categories effect on (**A**) stroke/systemic embolic event (SEE) and (**B**) major bleeding. ARISTOTLE indicates Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; CI, confidence interval; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate; and ROCKET AF, Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation.

Meta-Analysis of Data From the NOAC Trials

Since 2011, 4 phase III RCTs comparing vitamin K antagonist (ie, warfarin) and NOACs have been conducted (Table II in the online-only Data Supplement). Data about dabigatran and rivaroxaban were taken from supplementary materials from the main papers[24,25] and from the documents from regulatory submissions. Data on apixaban were taken from the article by Sandhu et al,[15] but no data on BMI classes were available for edoxaban from the main article, subanalyses, or regulatory documents. All studies considered and the data collected were of high-quality evidence, with a overall low risk of bias identified (Table III in the online-only Data Supplement). Thus,

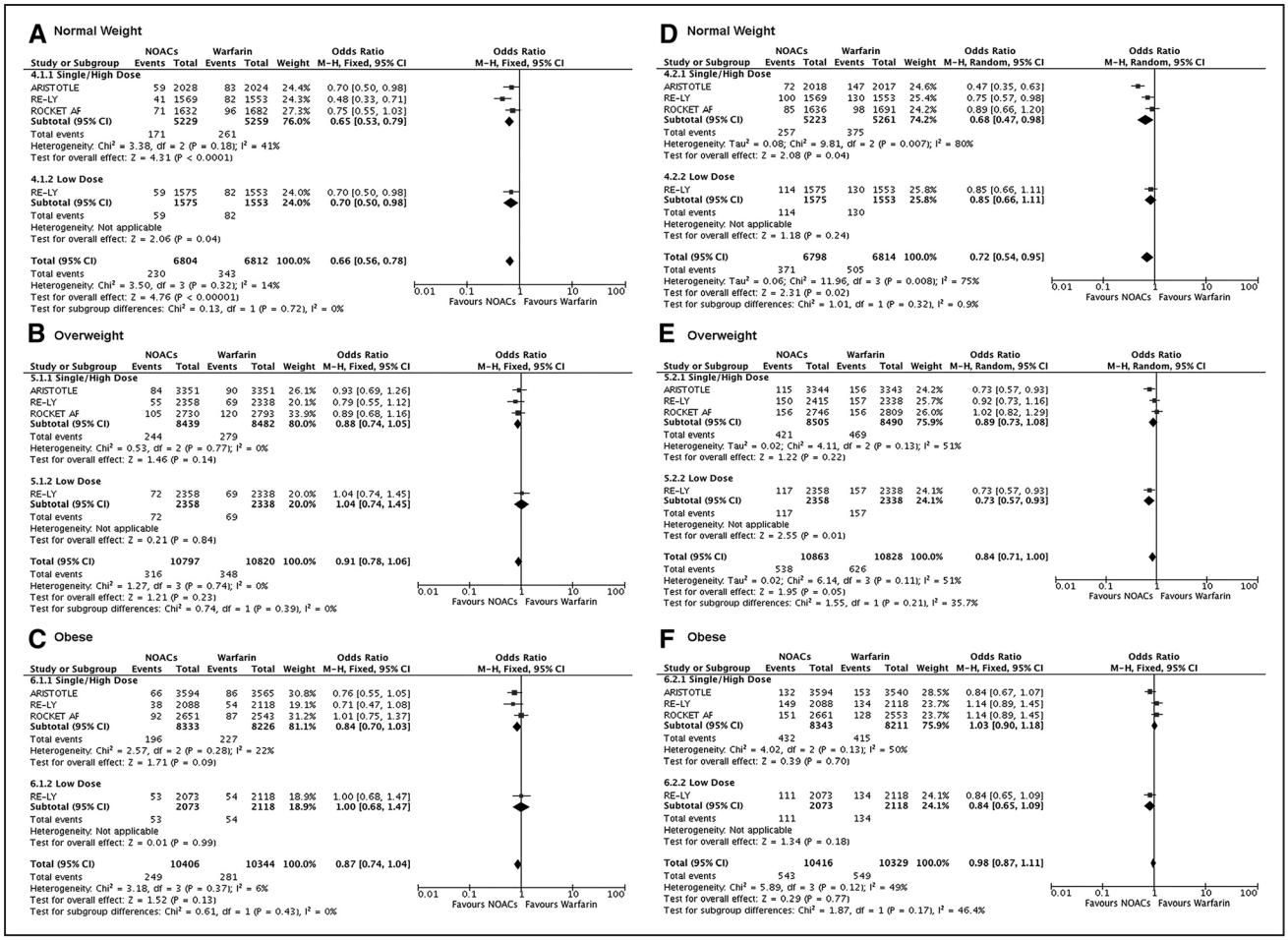

Figure 3. Treatment effect according to body mass index categories. Stroke/systemic embolic event (SEE): (**A**) normal weight; (**B**) overweight; and (**C**) obese. Major bleeding: (**D**) normal weight; (**E**) overweight; and (**F**) obese. ARISTOTLE indicates Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; CI, confidence interval; NOAC, non–vitamin K antagonist oral anticoagulants; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate; and ROCKET AF, Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation.

information on a total of 50 031 patients were available for analysis: of these 12 063 patients (24.1%) were in the normal weight category, 19 336 patients (38.6%) in the overweight category, and 18 632 patients (37.2%) in the obese category.

Compared with patients with normal weight, both overweight and obese patients had a lower risk for the occurrence of the stroke/SEE outcome (OR, 0.75; 95% CI, 0.66–0.84 and OR, 0.62; 95% CI, 0.54–0.70, respectively; Figure 2A). When comparing overweight and obese patients, obese ones were found to have a significantly lower risk of stroke/SEE (OR, 0.83; 95% CI, 0.73–0.94; Figure 2A).

For major bleeding (Figure 2B), a significant effect of the BMI categories was noted only when comparing normal weight with obese patients, with a lower risk for obese patients (OR, 0.84; 95% CI, 0.72–0.98), although a moderate degree of heterogeneity was found (I^2=58%). A significant treatment effect was found in normal weight patients (Figure 3A), with a lower risk for the stroke/SEE outcome in patients treated with NOACs (OR, 0.66; 95% CI, 0.56–0.78; P<0.00001). No significant difference between NOACs and warfarin was found in overweight and obese patients (Figure 3B and 3C).

For major bleeding (Figure 3D through 3F), both normal weight (OR, 0.72; 95% CI, 0.54–0.95; P=0.02) and overweight (OR, 0.84; 95% CI, 0.71–1.00; P=0.05) patients treated with NOACs had a lower risk for outcome occurrence compared with warfarin (Figure 3D and 3E). In overweight patients, a moderate heterogeneity was found (I^2=51). No difference was found in obese patients for the outcome of major bleeding (Figure 3F).

Discussion

Our systematic review of the literature seems suggestive of an obesity paradox in AF patients, in particular for all-cause and cardiovascular death outcomes, notwithstanding the presence of associated comorbidities or more intensive pharmacological treatments. This evidence seems to rise particularly from data from subgroup analyses of RCTs; conversely, observational studies with unadjusted analyses show the same evidence, but after statistical adjustments, the advantage of overweight and obese patients is less evident in most of the studies. Finally, an obesity paradox was evident for stroke/SEE outcome and major bleeding in the randomized trials of NOACs for stroke prevention in AF, with a treatment effect

favoring NOACs compared with warfarin that was significant for normal weight patients.

Publications on the obesity paradox have progressively increased in recent years, particularly among patient with cardiovascular disease.[4] A better prognosis, both in terms of all-cause and cardiovascular death, for overweight and obese patients has been reported for patients diagnosed with hypertension, coronary artery disease, congestive heart failure, and peripheral arterial disease.[6] Indeed, our systematic review shows several studies in AF patients in which an obesity paradox was evident. This phenomenon was most evident in RCT-derived cohorts, whereas in observational studies, the differences in adverse outcomes were no longer apparent after statistical adjustments for associated comorbidities in obese patients, leading to more intense risk factor management and hence improved outcomes.[11,22] Trial data show that the impact of BMI categories was attenuated by good anticoagulation control, again suggesting that optimized treatments could mitigate the obesity paradox.[12,14] Such evidence altogether reaffirms the necessity for a more holistic approach to AF management, which would include treating overweight and obese AF patients.[26]

In a recent meta-analysis of clinical studies examining the relationship between BMI, AF, and outcomes, with much narrower study selection criteria than our systematic review, Zhu et al[27] found that no significant increased risk for outcomes was associated with overweight and obese categories in AF patients. Even if overweight patients had a nonsignificant trend for lower risk for the adverse event (risk ratio, 0.91; 95% CI, 0.80–1.04; P=0.18), obese patients were still at lower risk for stroke/SEE when compared with normal weight patients (risk ratio, 0.84; 95% CI, 0.72–0.98; P=0.02). This seems reinforced by our analysis of the recent NOAC trials, where an obesity paradox was evident for the occurrence of stroke/SEE. A significant treatment effect favoring NOACs was found only for the normal weight patients and was nonsignificant for overweight and obese patients. In all the other studies reviewed, stroke and major bleeding alone were almost never affected by an obesity paradox.

In the non-AF patients, the relationship between BMI classes and stroke occurrence has been controversial. In a large meta-analysis comprising >2 millions of patients, both overweight and obese categories have associated with a higher risk of stroke occurrence.[28] Conversely, overweight and obese stroke patients may have a lower risk for death after stroke, whereas obese patients show a lower risk for stroke readmissions.[29]

Several considerations may explain the presence of this obesity paradox. First, the balance between lean and fat mass may be relevant, as rather than the BMI itself, the risk for adverse outcomes could be associated with the lean mass index. For example, in patients with stable coronary artery disease, the greatest risk for adverse events was mainly evident for those patients with low lean mass index when compared with those with high lean mass index, despite an overall high BMI.[30]

Another factor that may partially explain the lower risk associated with overweight and obesity could be age. In most studies, age was progressively lower in overweight and obese patients, compared with normal weight subjects. In most studies in which the obesity paradox was confirmed, a difference in age between the categories was more pronounced. The length of follow-up could also determine the occurrence of adverse events.[31] As evident from our results, those studies that failed to show an obesity paradox were those with the longest follow-up duration. Moreover, studies that only considered BMI at baseline did not examine the time-dependent changes nor factors that can attenuate and modify BMI, including physical activity and cardiorespiratory fitness. Indeed, the latter have been associated with lower weight and a lower risk of developing AF.[9,10]

Some specific considerations are needed for the Asian populations. Underweight is considered to be a risk factor for a higher risk of bleeding in Asian AF patients, leading to specific recommendations.[32] Our systematic review did not verify this perception, with the underweight category not being associated with an increased risk of major bleeding but conversely being associated with a higher risk for both cardiovascular and all-cause death. The Fushimi AF registry reported that AF patients with low body weight had a higher risk for stroke/SEE and all-cause death, whereas no influence was evident for major bleeding.[33] The mortality risk associated with being overweight has been confirmed in the general population.[34]

Limitations

The role of comorbidities and concomitant medications cannot be fully accounted for, despite multivariate adjustments. In observational studies, BMI reporting could be inaccurate. Hence, more studies specifically examining this issue, perhaps with time-dependent changes in BMI and investigating the balance between lean and fat body mass, are still needed to confirm the obesity paradox in AF. Furthermore, our exclusion of non-English studies and conference abstracts could have generated some selection bias. Our conclusions do not advocate the maintenance of a higher BMI in AF patients but emphasize the need of a holistic approach to AF management.

In conclusion, there may be an obesity paradox in AF patients, particularly for all-cause and cardiovascular death outcomes. Despite this, data from observational studies show that after full adjustments for baseline characteristics, an obesity paradox is no longer evident, highlighting the role of comorbidities and risk factor management in influencing the obesity paradox and thus leaving this question still partially unanswered. However, an obesity paradox was evident for stroke/SEE outcome in NOACs trials, with a treatment effect significantly favoring NOACs over warfarin in normal weight patients. Further evidence from large prospective studies may further clarify this relationship.

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Disclosures

Dr Proietti received small consultancy fee from Boehringer Ingelheim. Dr Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik,

Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. He is also a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. The other authors report no conflicts.

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