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ORIGINAL ARTICLE

Clinical Outcomes in Metabolically Healthy and Unhealthy Obese and Overweight Patients With Atrial Fibrillation: Findings From the GLORIA-AF Registry

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Abstract

Objective: To explore the association between metabolic status, body mass index (BMI), and natural history of patients with atrial fibrillation (AF).

Methods: The global, prospective GLORIA-AF Registry Phase II and III included patients with recent diagnosis of AF between November 2011 and December 2014 for Phase II and between January 2014 and December 2016 for Phase III. With this analysis, we categorized patients with AF according to BMI (normal weight [18.5 to 24.9 kg/m^2], overweight [25.0 to 29.9 kg/m^2], obese [30.0 to 60.0 kg/m^2]) and metabolic status (presence of hypertension, diabetes, and hyperlipidemia). We analyzed risk of major outcomes using multivariable Cox regression analyses; the primary outcome was the composite of all-cause death and major adverse cardiovascular events.

Results: There were 24,828 (mean age, 70.1±10.3 years; 44.6% female) patients with AF included. Higher BMI was associated with metabolically unhealthy status and higher odds of receiving oral anticoagulants and other treatments. Normal-weight unhealthy patients showed a higher risk of the primary composite outcome (adjusted hazard ratio [aHR], 1.20; 95% CI, 1.01 to 1.42) and thromboembolism, whereas a lower risk of cardiovascular death (aHR, 0.35; 95% CI, 0.14 to 0.88) and major adverse cardiovascular events (aHR, 0.56; 95% CI, 0.33 to 0.93) was observed in metabolically healthy obese individuals. Unhealthy metabolic groups were also associated with increased risk of major bleeding (aHR, 1.51 [95% CI, 1.04 to 2.20] and aHR, 1.96 [95% CI, 1.34 to 2.85] in overweight and obese groups, respectively).

Conclusion: Increasing BMI was associated with poor metabolic status and with more intensive treatment. Prognosis was heterogeneous between BMI groups, with metabolically unhealthy patients showing higher risk of adverse events.

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The prevalence of overweight and obese individuals has reached epidemic proportions during the last decades, especially in Western countries.[1] Up to 50% of adults living in Europe fit this category.[2] Obesity has been associated with risk factors for cardiovascular diseases (CVDs), such as elevated blood pressure, dyslipidemia, and high glucose levels.[3,4] Therefore, adults who are overweight or obese are more prone to development of CVDs and hence have higher risk of death.[3]

Atrial fibrillation (AF), the most common serious cardiac arrhythmia, is a major cause of morbidity and mortality worldwide, exposing those affected to a 5-fold increased risk of stroke.[5] Many cardiovascular risk

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factors are associated with incident AF and adverse outcomes in patients with AF diagnosis. Of those, obesity and metabolic syndrome are 2 of the most important contributing factors to the development of AF.[6,7]

Proactive management of comorbidities and attention to lifestyle factors have been advocated to achieve reduction in CVDs (including incident AF) and to reduce the risk of adverse events associated with AF.[8-12] Several guidelines indeed recommend healthy lifestyle habits to reduce the risk for development of AF.[13] Lifestyle changes are part of the holistic and integrated care approach to AF management as encompassed in the AF Better Care (ABC) pathway.[14] Following the ABC pathway has been associated with improved outcomes in AF patients[15] and is now recommended in guidelines.[16,17]

Nonetheless, several studies and a meta-analysis have reported an inverse relationship between obesity and cardiovascular prognosis. Specifically, overweight and mildly obese patients with established CVDs have better short- and moderate-term prognoses compared with leaner patients. This phenomenon, referred to as the obesity paradox,[6,18,19] has been described for many CVDs, including AF.[20,21]

Because subcutaneous distribution of fat along with its metabolic activity was proposed to be linked to atherosclerosis,[22] several studies have introduced the concept of metabolic status to provide a better stratification of CVD risk[23-25]; for example, a metabolically healthy obese patient is an obese patient with no features of metabolic syndrome, such as hypertension, diabetes mellitus (DM), or hyperlipidemia.[26,27] It has been hypothesized that the interplay between metabolic status and obesity can lead to heterogeneous risk of CVD. However, there is controversial evidence for an increased risk of adverse outcomes in metabolically unhealthy obese patients compared with those who are metabolically heathy obese.[23,28] Metabolically unhealthy obese patients have been found to have higher risk of ischemic stroke, myocardial infarction, and new-onset AF compared with metabolically heathy obese patients.[24] Nonetheless, the effect of metabolic status on the risk of adverse events in patients with established AF remains unknown. It is also unknown whether the obesity paradox could be related to metabolic status.

In this study, we analyzed the associations between body mass index (BMI) categories (normal, overweight, and obese), metabolic status, and risk of adverse events using data from the prospective multicenter Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF).

METHODS

The GLORIA-AF is a global, multicenter prospective registry, structured in 3 phases, that explored the long-term safety and effectiveness of dabigatran in real-world patients with AF. Details of the study design of GLORIA-AF and the primary analysis comparing dabigatran with vitamin K antagonists (VKAs) and other non−vitamin K oral anticoagulants (NOACs) have been published elsewhere.[29-31] Briefly, consecutive patients with new-onset nonvalvular AF and a CHA_2DS_2-VASc score of 1 or more were enrolled between November 2011 and December 2014 for Phase II and between January 2014 and December 2016 for Phase III. All participants who received dabigatran during Phase II were observed for major outcomes for 2 years, whereas all participants enrolled during Phase III were followed up for 3 years, regardless of antithrombotic treatment received.

Inclusion and Exclusion Criteria

Detailed inclusion and exclusion criteria have been published elsewhere.[30] Eligible patients for GLORIA-AF registry were adults (age $\geq$18 years) with a recent diagnosis of AF ($<$3 months before enrollment or $<$4.5 months in Latin America) and a CHA_2DS_2-VASc score of 1 or more who provided written informed consent. Main exclusion criteria were AF due to a reversible cause, presence of a mechanical heart valve (or expected valve replacement), patients who

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have received more than 60 days of VKA treatment in their lifetime, patients with a medical indication for oral anticoagulant (OAC) treatment other than AF, and patients with a life expectancy of less than 1 year. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Local institutional review boards at each participating site gave ethical approval.

For this analysis, we included patients with BMIs between 18.5 and 60 kg/m^2 and with data on metabolic status (ie, hypertension, DM, and hyperlipidemia) and follow-up status for the primary outcome. BMI was calculated by dividing the individual's body weight in kilograms by the square of height in meters. Normal-weight patients were those who had a BMI of 18.5 to 24.9 kg/m^2, overweight patients were those having a BMI of 25 to 29.9 kg/m^2, and obese patients were defined as having a BMI of 30.0 to 60 kg/m^2. Metabolic status was defined on the basis of hypertension, DM, and hyperlipidemia as recorded by investigators in the electronic case report form. Metabolically unhealthy status was defined according to the presence of at least 1 of these comorbidities, consistent with the definition used in other previous studies.[24] Patients without hypertension, DM, or hyperlipidemia were considered metabolically healthy. According to these definitions, we identified 6 groups: metabolically healthy normal-weight patients; metabolically unhealthy normal-weight patients; metabolically healthy overweight patients; metabolically unhealthy overweight patients; metabolically healthy obese patients; and metabolically unhealthy obese patients. Drugs prescribed at baseline were obtained from electronic case report forms.

Follow-up and Outcomes

Details about follow-up and outcomes for GLORIA-AF Phase II and Phase III were reported elsewhere.[30,32] For this analysis, we defined our primary outcome as the composite of all-cause death and major adverse cardiovascular event (MACE; cardiovascular death, stroke, and myocardial infarction). We assessed the following secondary exploratory outcomes, according to weight categories and metabolic status: all-cause death, cardiovascular death, MACE, stroke (including hemorrhagic and ischemic stroke as well as strokes of uncertain classification), thromboembolism (as the composite of stroke, transient ischemic attack, and other non−central nervous system thromboembolism), and major bleeding (defined according to the International Society of Thrombosis and Haemostasis classification, that is, overt bleeding associated with a hemoglobin reduction of at least 20 g/L or leading to at least 2-unit of blood transfusion, symptomatic bleeding in a critical organ, or life-threatening or fatal bleeding).

Statistical Analyses

Normal and nonnormal distributed continuous variables were reported according to mean and standard deviation or median and interquartile range and were compared with appropriate parametric (including *t*-test and analysis of variance) and nonparametric (including Mann-Whitney *U* and Kruskal-Wallis) tests. Categorical variables, reported as frequencies and percentages, were compared by χ^2 testing. Multivariable logistic regression was performed to analyze associations between BMI categories with metabolically unhealthy status and with prescription of the most relevant drugs used for stroke prevention of AF (OACs) and for the treatment of metabolic status determinants (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, oral hypoglycemic agents, and statins).

Results were reported as adjusted odds ratio (aOR) and 95% CI; multivariable Cox regression analyses were performed to evaluate the association between the groups and the risk of major outcomes, and results were reported as adjusted hazard ratio (aHR) and 95% CI. All models were adjusted for age, sex, type of AF, history of coronary artery disease, chronic heart failure, history of ischemic stroke/transient ischemic attack, and peripheral artery disease. Logistic regression models for the prescription of drugs were further adjusted for the determinants of metabolic status (ie, hypertension,

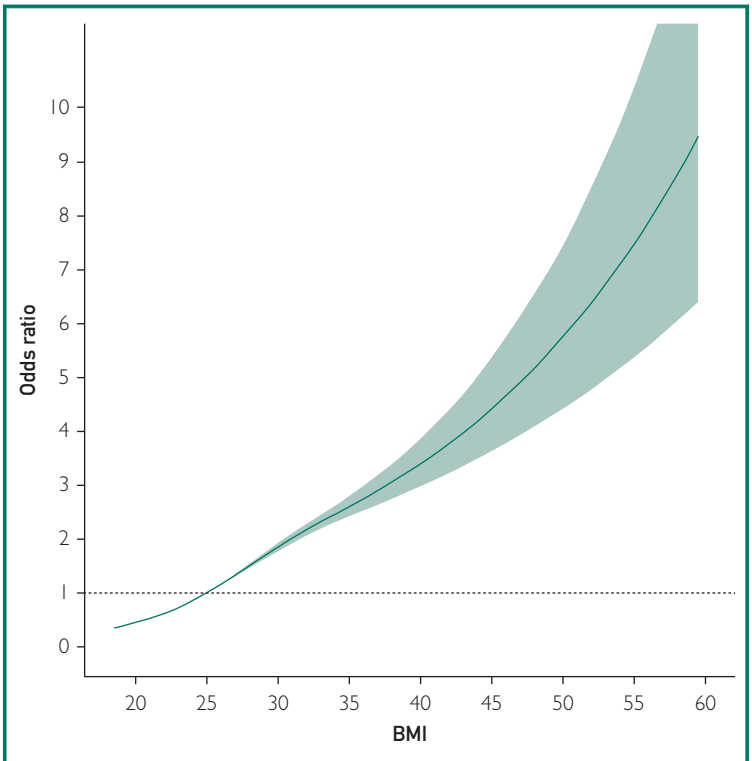

FIGURE 1. Association between body mass index (BMI) and odds ratio of metabolically unhealthy status.

DM, hyperlipidemia). Cox regression models were further adjusted for the use of OACs.

We evaluated the association between BMI, modeled as a continuous, nonlinear variable (using a restricted cubic spline with 3 knots placed at default knot locations), and metabolically unhealthy status. We evaluated interactions between BMI and metabolic status on the risk of primary outcome. For these analyses, BMI of 25 kg/m^2 was taken as reference.

Kaplan-Meier curves for the primary composite outcome were reported according to metabolic status and weight categories. Survival distributions were compared using the log-rank test.

We performed sensitivity analyses for the risk of major outcomes. First, we considered only patients recruited in Phase III of GLORIA-AF. Second, we used various BMI cutoffs for Asian patients (as defined by self-reported ethnicity), with Asian-specific cutoffs proposed in previous studies[33,34]: normal weight if BMI was 18.5 to 22.9 kg/m^2, overweight if BMI was 23 to 24.9 kg/m^2, and obese if BMI exceeded 25 kg/m^2. Standard cutoffs were used for non-Asian individuals. In a third sensitivity analysis, we evaluated various definitions of metabolically unhealthy status, specifically according to the presence of 2 or more of the following: hypertension, DM, and hyperlipidemia. In a final sensitivity analysis, we considered overweight and obese patients as a single group.

A 2-sided *P* of less than .05 was regarded as statistically significant. All analyses were performed using R 4.0.3 (R Foundation for Statistical Computing).

RESULTS

Of 36,617 patients originally enrolled in Phase II and Phase III of GLORIA-AF, we included 24,828 (mean age, 70.1±10.3 years; 44.6% female) in this analysis, according to the inclusion criteria reported before. Of these, 6893 (27.8%) were normal weight, 9669 (38.9%) were overweight, and 8266 (33.3%) were obese. Regarding metabolic status, 4067 (16.4%) were metabolically healthy, whereas 20,761 (83.6%) were metabolically unhealthy.

Baseline characteristics and treatments according to the 6 groups of analysis are reported in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org). The most represented group was the overweight unhealthy (8161 [32.9%]); conversely, only 781 patients (3.1%) were metabolically healthy obese. Across each BMI group, metabolically unhealthy patients were older, with a higher burden of comorbidities and thromboembolic and bleeding risk. Consistently, use of OACs was higher among metabolically unhealthy patients. Use of NOACs was lowest in the normal-weight healthy patients (58.3%) and highest in the obese unhealthy subgroup (72.1%).

Associations Between BMI Categories, Metabolic Status, and Drug Prescription

Compared with normal weight, overweight and obese BMI categories were associated with metabolically unhealthy status at

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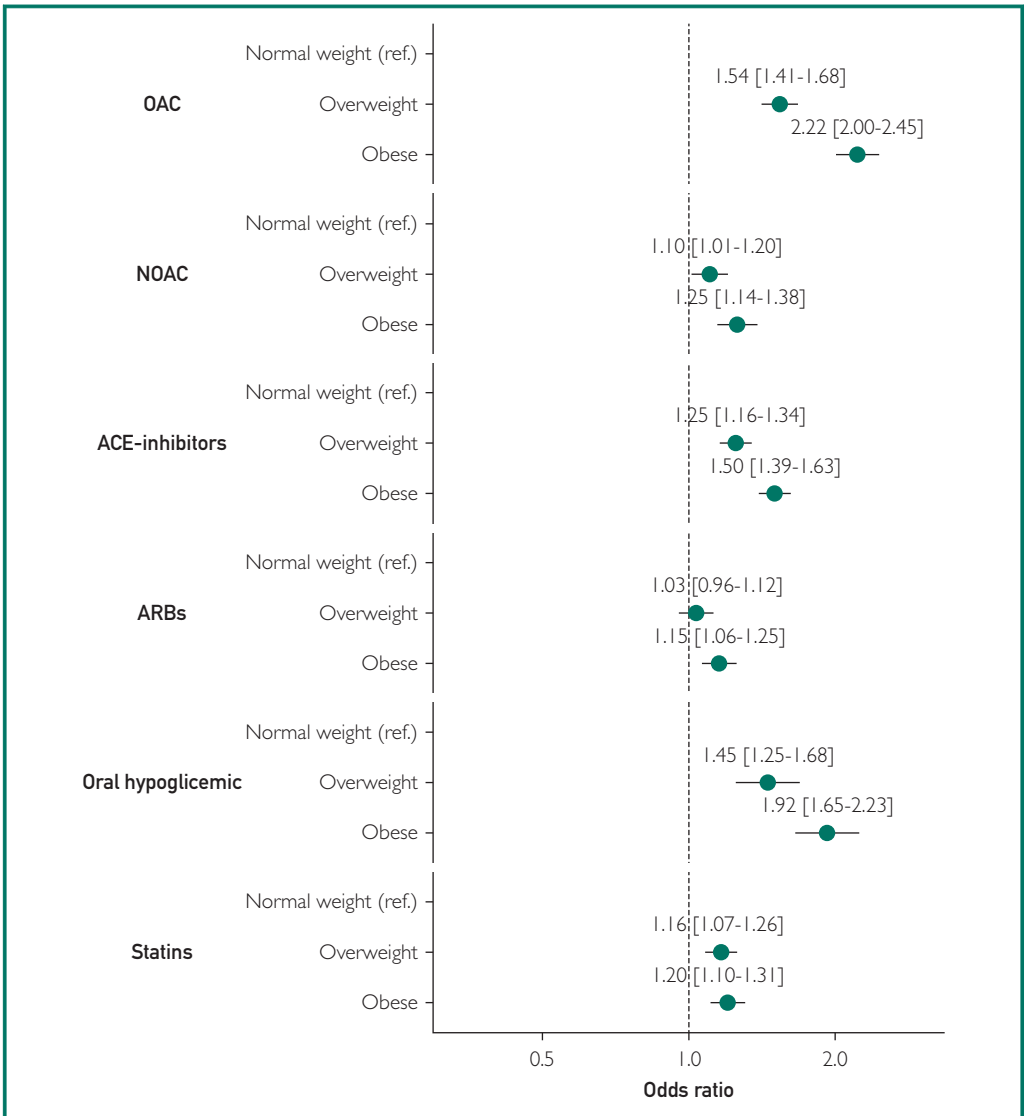

FIGURE 2. Logistic regression analysis on the prescription of drugs at baseline, according to weight categories. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NOAC, non—vitamin K oral anticoagulant; OAC, oral anticoagulant.

multivariable logistic regression analysis (aOR, 1.94 [95% CI, 1.79 to 2.11] and aOR, 3.84 [95% CI, 3.49 to 4.23], respectively) after adjustment for age, sex, type of AF, history of heart failure, coronary artery disease, history of stroke/transient ischemic attack, and peripheral artery disease. Considering BMI as a continuous variable, there was a nonlinear relationship between increasing BMI and the odds of being metabolically unhealthy (Figure 1).

Patients in a higher BMI category were more likely to receive almost all drugs investigated (Figure 2) after adjustment for age, sex, type of AF, history of heart failure, coronary artery disease, history of stroke/transient ischemic attack, peripheral artery disease, and determinants of metabolic status (hypertension, DM, hyperlipidemia). Obese patients were twice as likely as those of normal weight to receive OACs and oral hypoglycemic drugs and 25% more

likely to receive NOACs compared with VKAs.

Adverse Outcomes According to Weight Category and Metabolic Status

During a median follow-up of 36.2 (interquartile range, 26.3-37.6) months, 2813 primary outcome events occurred (all-cause death and MACE). Kaplan-Meier curves for the primary composite outcomes are reported in the Supplemental Figure (available online at http://www.mayoclinicproceedings.org). There was better survival for metabolically healthy participants across each stratum of BMI. Conversely, a progressively worse survival was observed on the basis of weight category.

Cox regression models on the risk of major outcomes according to metabolic status and BMI groups are reported in the Table. Compared with normal-weight healthy individuals, normal-weight unhealthy individuals were at higher risk of the primary composite outcome (aHR, 1.20; 95% CI, 1.01 to 1.42). No significant differences were observed for the other groups, although a trend toward lower risk of the primary composite outcome was observed for obese healthy participants (aHR, 0.73; 95% CI, 0.53 to 1.02).

Regarding secondary outcomes, normal-weight metabolically unhealthy participants showed a greater risk of thromboembolism (aHR, 1.41; 95% CI, 1.03 to 1.93), whereas the obese healthy group had a reduced risk of cardiovascular death (aHR, 0.35; 95% CI, 0.14 to 0.88) and MACE (aHR, 0.56; 95% CI, 0.33 to 0.93). All unhealthy subgroups had greater risk of major bleeding, with greatest risk observed in the obese unhealthy group (Table).

Figure 3 shows the interaction between BMI and metabolic status on the risk of the primary composite outcome. There was a nonstatistically significant J-shaped relationship in metabolically unhealthy participants and higher hazards observed for subgroups with BMI below 25 kg/m^2 and above 35 kg/m^2, consistent with the primary analyses. A nonstatistically significant interaction (P=.186) between BMI and metabolic status was observed on the risk of the primary outcome.

Sensitivity Analysis

In the first sensitivity analysis, we restricted the cohort to patients enrolled in Phase III of the GLORIA-AF Registry (n=20,224). The results of this analysis are reported in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org) and provided broadly consistent estimates compared with our primary analysis.

In the second sensitivity analysis, we considered various cutoffs for the definition of normal-weight, overweight, and obese subgroups for the Asian patients (identified according to their self-reported ethnicity).[33,34] As expected, more patients were categorized as obese (9871 [39.8%]). Cox regression for this analysis is reported in Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org). With ethnic-specific cutoffs for BMI, obese healthy patients were found to have lower risk of the primary composite outcome (aHR, 0.65; 95% CI, 0.48 to 0.89). These patients were also at lower risk of secondary outcomes, including all-cause death, cardiovascular death, MACE, and ischemic stroke. Overweight healthy patients also had a marginally significant lower risk of stroke and MACE (aHR, 0.70 [95% CI, 0.49 to 1.00; P=.049] and aHR, 0.58 [95% CI, 0.34 to 1.00; P=.049], respectively). In the unhealthy groups, normal weight showed an increased risk of all-cause death, and both normal-weight and obese unhealthy groups showed a higher risk of major bleeding events.

We repeated our analysis defining being metabolically unhealthy as the presence of at least 2 of the following: hypertension, DM, and hyperlipidemia. Results are reported in Supplemental Table 4 (available online at http://www.mayoclinicproceedings.org). We found that overweight and obese healthy patients had lower risk of the primary outcome compared with normal-weight healthy patients (aHR, 0.81 [95% CI, 0.71 to 0.92] and aHR, 0.81 [95% CI,

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TABLE. Adjusted Cox Regression Analysis for the Risk of Primary and Secondary Outcomes According to Weight Categories and Metabolic Status

	Normal-weight healthy	Normal-weight unhealthy		Overweight healthy		Overweight unhealthy		Obese healthy		Obese unhealthy	
		aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*
Primary outcome											
All-cause death and MACE	Ref.	**1.20 (1.01-1.42)**	**.039**	0.84 (0.66-1.07)	.16	0.94 (0.80-1.12)	.50	0.73 (0.53-1.02)	.063	1.05 (0.88-1.25)	.58
Secondary outcomes											
All-cause death	Ref.	1.19 (0.98-1.45)	.079	0.94 (0.72-1.24)	.67	0.92 (0.75-1.11)	.38	0.71 (0.48-1.05)	.087	1.02 (0.83-1.24)	.87
CV death	Ref.	1.29 (0.91-1.83)	.15	1.00 (0.62-1.60)	>.99	1.01 (0.72-1.43)	.95	**0.35 (0.14-0.88)**	**.026**	1.07 (0.75-1.51)	.72
MACE	Ref.	1.21 (0.95-1.54)	.12	0.73 (0.52-1.04)	.083	1.01 (0.80-1.28)	.95	**0.56 (0.33-0.93)**	**.024**	1.08 (0.85-1.37)	.55
Stroke	Ref.	1.34 (0.94-1.91)	.11	0.71 (0.42-1.20)	.20	1.05 (0.74-1.49)	.79	0.55 (0.25-1.17)	.12	1.07 (0.75-1.53)	.71
Thromboembolism	Ref.	**1.41 (1.03-1.93)**	**.033**	0.83 (0.53-1.30)	.42	1.17 (0.86-1.59)	.32	0.75 (0.41-1.37)	.35	1.14 (0.83-1.56)	.43
Major bleeding	Ref.	**1.65 (1.12-2.42)**	**.011**	1.16 (0.70-1.92)	.57	**1.51 (1.04-2.20)**	**.031**	1.36 (0.75-2.46)	.31	**1.96 (1.34-2.85)**	**<.001**

aHR, adjusted hazard ratio; CV, cardiovascular; MACE, major adverse cardiovascular event; Ref., reference group. Bold text depicts statistically significant results at $P < .05$ level. Adjusted for age, sex, type of atrial fibrillation, history of coronary artery disease, use of oral anticoagulant, chronic heart failure, history of ischemic stroke/transient ischemic attack, and peripheral artery disease.

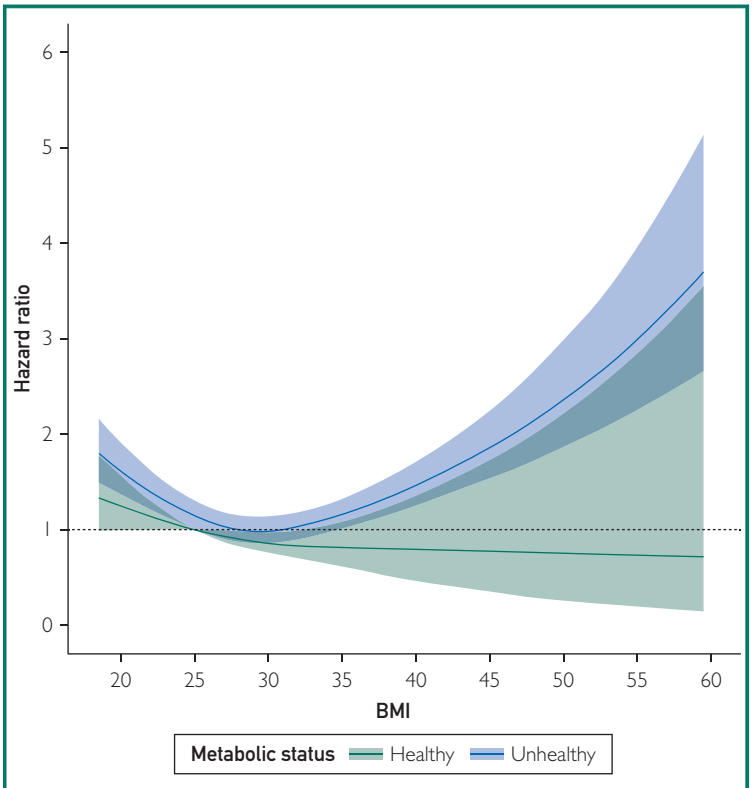

FIGURE 3. Interaction between body mass index (BMI) and metabolic status on the risk of the primary composite outcome.

0.69 to 0.94], respectively); overweight healthy also had lower risk of all-cause death (aHR, 0.85; 95% CI, 0.74 to 0.99), MACE (aHR, 0.77; 95% CI, 0.64 to 0.92), and stroke (aHR, 0.74; 95% CI, 0.57 to 0.98). Normal-weight unhealthy patients had a higher risk of the primary outcome (aHR, 1.22; 95% CI, 1.06 to 1.40) as well as of all-cause death (aHR, 1.23; 95% CI, 1.05 to 1.44), MACE (aHR, 1.27; 95% CI, 1.04 to 1.54), and thromboembolism (aHR, 1.34; 95% CI, 1.04 to 1.71) compared with normal-weight healthy patients, whereas all groups (except for overweight healthy patients) showed higher risk of major bleeding.

Finally, we performed a sensitivity analysis considering overweight and obese patients as a single group. Results of this analysis are reported in Supplemental Table 5 (available online at http://www.mayoclinicproceedings.org) and were consistent with those of the primary analysis, with the overweight/obese healthy group showing a strong trend toward lower risk of the primary composite outcome (aHR, 0.80; 95% CI, 0.65 to 1.00) and a lower risk of MACE (aHR, 0.68; 95% CI, 0.49 to 0.93). Normal-weight unhealthy and overweight/obese unhealthy groups were associated with increased risk of major bleeding (aHR, 1.65 [95% CI, 1.12 to 2.43] and aHR, 1.71 [95% CI, 1.19 to 2.46], respectively).

DISCUSSION

In this analysis of the GLORIA-AF registry, we found that metabolically unhealthy status (presence of hypertension, DM, or hyperlipidemia) is common in patients with AF. Overweight and obesity are associated with worse metabolic status and higher intensity of treatment for both thromboembolic risk prevention and management of comorbidities. Unhealthy metabolic status was associated with increased risk of the primary outcome in normal-weight individuals, with a trend in obese patients but not in overweight patients. For healthy participants, an obesity paradox was observed for cardiovascular secondary outcomes. Finally, metabolically unhealthy patients, regardless of their BMI category, were associated with an increased risk of major bleeding, highlighting the importance of metabolic status on the hemorrhagic risk.

This study, using data from a large global, prospective, and contemporary registry of patients with AF, provides the largest assessment to date of the association between metabolic status, BMI levels, and prognosis of patients with AF. The prevalence of cardiovascular risk factors as well as of CVDs is higher in obese patients. However, a good prognosis has been reported in relation to outcomes in overweight and obese patients with established CVD[35] compared with normal-weight patients, thus leading to the concept of obesity paradox. Indeed, the benefit observed at higher BMI levels seems to depend on the grade of obesity, being significant only for overweight patients.[36]

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Rather than obesity's being a simple binary/categoric diagnosis, metabolic status has been proposed as a potential explanation for the obesity paradox. Several studies have instead observed higher risk of cardiovascular events in metabolically healthy obese compared with normal-weight participants.[28,37,38] Nonetheless, there remains the lack of a universal definition of metabolically healthy status, perhaps representing a reason for the different strengths of the association observed between obesity, metabolic status, and risk of adverse outcomes.[39]

Indeed, the interplay between metabolic status and BMI in patients with AF is still not fully understood. Importantly, most studies that explore the obesity paradox in AF do not consider metabolic status.[21,40-42] A more comprehensive understanding of the interplay between obesity, metabolic status, and outcomes in patients with AF is needed to better define treatment goals and intervention and to improve outcomes.

Our results show how increasing BMI, as a continuous variable, is associated with poor metabolic status in patients with AF, with obese patients presenting almost 4-fold higher odds of being metabolically unhealthy. Furthermore, overweight and obese patients were treated more aggressively, as encompassed by 2-fold higher odds of receiving OACs, in agreement with another analysis,[43] and a higher likelihood of being treated with other drugs that are usually administered to treat hypertension, DM, and hyperlipidemia. These findings suggest how increasing BMI may influence the treating physicians' perception of the need for prescription, leading to more intensive treatment patterns, which may ultimately improve prognosis.

Indeed, our survival analysis finds that compared with normal-weight metabolically healthy participants, those metabolically unhealthy had a higher risk of the primary composite outcome. Nonetheless, a trend toward lower risk of the primary outcome was observed as BMI increased, consistent with the obesity paradox observed for cardiovascular outcomes (ie, MACEs and cardiovascular death).

Several hypotheses can be drawn to explain these results. First, obese and overweight patients were younger than normal-weight healthy participants; the intensity of medical treatments was higher as the BMI increased, suggesting that these patients may have been diagnosed earlier and may have received more comorbidities-directed management than normal-weight patients, also with a more intensive treatment approach (and tighter treatment goals). This is consistent with what has been observed in other clinical scenarios, such as coronary artery disease.[44] Second, baseline thromboembolic and hemorrhagic risks—as encompassed by CHA_2DS_2VASc and HAS-BLED scores—were slightly lower in overweight and obese participants compared with normal-weight individuals across the metabolic status strata. Furthermore, the amount of physical activity undertaken by the participants might have been different in the included patients, given that overweight or obese patients who exercise may have a better prognosis than normal-weight patients who do not[45-49]; indeed, it is possible that physical activity would be more likely to be recommended to overweight and obese patients to reduce their weight, and studies highlight the importance of the evaluation of cardiorespiratory fitness,[48] especially in metabolically healthy obese patients.[50]

Our study found that poor metabolic status critically influenced the risk of major bleeding, with all unhealthy groups being at higher risk of hemorrhagic events during follow-up. These results are consistent with the variables used to define metabolic status, including hypertension and DM, which are known risk factors for hemorrhagic events, as well as with metabolically unhealthy patients being most treated with OACs. Of note, we found that the highest risk was reported for obese unhealthy patients, underlining that the combination of poor metabolic status and high BMI may have a specific detrimental effect on the risk of major bleeding events. Furthermore, recommendations on the use of NOACs underline how data on effectiveness and

safety of NOACs in patients with BMI above 40 kg/m^2 are less robust,[51] thus confirming the uncertainties in this group of patients with potentially inappropriate use of high-dose of OACs.

Our sensitivity analyses found how the definition of obesity and metabolic status may influence these associations. Both the implementation of Asian-specific cutoffs for defining overweight and obesity (adoption of which has been repeatedly debated)[34,52] and the use of stricter criteria for defining metabolically unhealthy status showed enhancement of the obesity paradox effect in the metabolically healthy groups, especially on the risk of cardiovascular outcomes.

Taken together, our results have several clinical implications. First, the relationship between obesity and metabolic status is intertwined and complex and is influenced by ethnicity and the overall burden of factors that impair metabolic status. Moreover, this relationship heterogeneously affects both treatment patterns and the risk of major outcomes. Furthermore, our findings suggest that if an obesity paradox exists, this may be explained by more intensive treatment of overweight and obese patients and may also not apply to metabolically unhealthy individuals, who therefore require further efforts and specific attention to improve their prognosis. Moreover, we reinforce the need for comprehensive and integrated approaches to the treatment of patients with AF, which includes the management of associated comorbidities as well as lifestyle changes and weight loss. Indeed, the implementation of the ABC pathway, which has already been proved effective in reducing outcomes in patients with AF,[53] including major bleeding events,[15] appears crucial in patients with AF, especially in those who have both obesity and poor metabolic status, to improve their prognosis, as already reported in clinically complex patients.[54]

Our study provides a comprehensive overview on the relationship between BMI, metabolic status, treatment patterns, and prognosis using a large, global, and contemporary cohort of patients newly diagnosed with AF. This allowed us to stratify the patients into 6 subgroups and to provide a homogeneous and pragmatic definition of metabolic status across a large cohort of patients with AF. Nevertheless, our study has several limitations. First, some patients were excluded from the analysis because of lacking data on some characteristics needed to identify BMI or metabolic status. Moreover, our definition of metabolic status took into consideration the presence of at least 1 comorbidity between hypertension, DM, and hyperlipidemia. We had no data for biomarkers (eg, cholesterol levels, hemoglobin A_{1c}), and therefore we were not able to define metabolic status according to these variables. Of note, previous studies have followed a similar approach (using baseline comorbidities) to define metabolic status,[24] thus being consistent with our methods. Nonetheless, this may represent an indirect evaluation of metabolic status, and further studies specifically designed to assess this research question are required to confirm whether the inclusion of more specific biomarkers or definition of metabolic status may lead to similar results.

We have performed a sensitivity analysis to investigate a different (and stricter) definition of metabolic status to provide insights on potential differences arising from different definitions of metabolic health. Moreover, although we have provided multivariable regression models, which accounted for the most common comorbidities found among patients with AF, we cannot exclude the contribution of unaccounted confounders in the results observed. Furthermore, our results on secondary outcomes were not adjusted for multiple comparisons or for competing risk events and therefore should be interpreted with caution and regarded as exploratory. Finally, potential ethnic and geographic differences may exist in the relationship between BMI, metabolic status, and natural history of AF that may have influenced results. Nonetheless, we have provided a sensitivity analysis using Asian-specific cutoffs for BMI, with the aim of providing insights on the potential ethnic-based differences in the definition of overweight and obesity.

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CONCLUSION

In this large prospective global registry, metabolically unhealthy status was common among patients with AF and associated with high BMI levels. Unhealthy normal-weight participants were associated with a higher risk of the primary outcome of all-cause death and MACE as well as major bleeding. An obesity paradox was observed in healthy patients for secondary cardiovascular outcomes.

POTENTIAL COMPETING INTERESTS

G.F.R. reports consultancy for Boehringer Ingelheim and an educational grant from Anthos, outside the submitted work. No fees are directly received personally. M.P. is investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 899871. G.Y.H.L. has been consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Anthos, and Daiichi-Sankyo. No fees are directly received personally. All the disclosures happened outside the submitted work. G.Y.H.L. is co—principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 899871. All other authors have nothing to report.

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Profs Lip and Huisman are co-chairs of the GLORIA-AF registry program.

Drs Corica and Romiti are co—first authors.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ABC pathway,** AF Better Care pathway; **AF,** atrial fibrillation; **aHR,** adjusted hazard ratio; **aOR,** adjusted odds ratio; **BMI,** body mass index; **CVD,** cardiovascular disease; **DM,** diabetes mellitus; **GLORIA-AF,** Global Registry on Long-Term Oral Anti-thrombotic Treatment in Patients with Atrial Fibrillation; **MACE,** major adverse cardiovascular event; **NOAC,** non—vitamin K oral anticoagulant; **OAC,** oral anticoagulant; **VKA,** vitamin K antagonist

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