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Obesity Paradox and 12 Month Outcome in Patients with Atrial Fibrillation

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Background and aim. Obesity increases the risk of atrial fibrillation (AF) while it may impact the outcome of patients with AF. The clinical implications of this relationship are not completely clear. We aimed to analyze the association of traditional anthropometric measures of excessive adiposity with 12 month case fatality rate (CFR) in patients with AF.

Methods. This was a multicenter, longitudinal, observational study on adults with documented AF, excluding records of AF secondary to reversible causes. Anthropometric variables were registered at baseline, and a central committee validated the 12 month outcomes.

Results. We studied 1193 patients (median age: 69.14 years, 55.2% women). At baseline, rhythm control was established for 476 (39.9%) subjects, while frequency control was offered to 717 (60.1%) participants. The 12 month all-cause CFR was 8.9%. A high basal body mass index (BMI), waist-to-height ratio (WHtR) and waist circumference (WC) were associated with lower CFR in bivariate analyses. In a Cox-proportional hazards model, variables associated with 12 month all-cause CFR were BMI categories (HR: 0.736, 95% CI: 0.584−0.928), chronic heart failure (HR: 1.738, 95% CI: 1.127−2.680), chronic kidney disease (HR: 2.269, 95% CI: 1.162−4.429) and carotid stenosis >50% (HR: 5.342, 95% CI: 1.661−17.181).

Conclusion. The risk of death at one year in patients with AF is inversely associated with a high BMI and directly associated with the presence of chronic kidney disease, carotid stenosis, and chronic heart failure in this cohort of patients with AF. The causes and implications of this apparent obesity paradox should be addressed in the future.

Key Words: Arrhythmias, Antiarrhythmic, Atrial fibrillation, Mexico, Obesity paradox, Outcome, Registry.

Introduction

Atrial fibrillation (AF) is the most frequent rhythm disorder associated with age (1). While the prevalence is about 0.5% in people aged <50 years, it can reach up to 15% in people aged 80 years and older (1−3). As a consequence, the prevalence of AF is expected to increase worldwide due to the improvement in life expectancy and the rise of risk factors for AF in vulnerable populations. AF implies a significant risk of morbidity and mortality due to cerebral and systemic embolism (3).

On the other hand, obesity has reached pandemic proportions, which in part relates to the recent rise in other associated conditions, such as diabetes mellitus, dyslipidemia, osteoarthritis, and atherothrombotic disease (4). Obesity, also an established risk factor for AF (5−7), is

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biologically conceptualized as ''excessive'' adiposity, but clinically and epidemiologically defined by a high body mass index (BMI) (8). The coexistence of a high BMI with AF can reach a frequency of up to 70% (9). Nonetheless, the impact of obesity on several outcomes of clinical relevance needs more exploration, especially considering that a high BMI is a risk modifier in patients with AF. Furthermore, BMI is an imperfect proxy of body adiposity, and other anthropometric measures may reflect better the body fat content and the adverse outcomes associated with obesity. This analysis aimed to establish the relationship between traditional anthropometric measures and 12 month all-cause case fatality rate (CFR) in patients with AF.

Methods

The design of the ReMeFa registry, the selection criteria, objectives, and procedures were published elsewhere (10,11). In short, ReMeFA was a multicenter, prospective, observational study on the treatment of AF in Mexican patients seen by general practitioners or specialists. The main objective was to describe the demographic and clinical characteristics of patients receiving treatment for rhythm control or treatment for rate control, as well as the management of risk factors. Secondary objectives were considered to evaluate the clinical status of the patients at 12 ($\pm$3) month follow-up, and to explore potential factors that modify the risk of outcomes such as all-cause death, cardiovascular death, hospitalizations for rhythm/frequency control or hospitalizations due to cardiovascular and atherothrombotic complications. A central Institutional Review Board and Ethics Committee provided the revision and approval of the study protocol. For five participating centers, it was required an additional local protocol review. Signed informed consent was required for each case registered.

A minimum of 864 patients was estimated as the sample size necessary to reach primary objectives, with a statistical power of 80%. Considering ''lost to follow-up'' cases of up to 25% per year, the study began with the intention of recording a minimum of 1152 patients. Data were recorded prospectively during a baseline visit, a follow-up visit at 6 $\pm$ 2 months, and a second follow-up visit at 12 $\pm$ 3 months. We included patients with age $\geq$18 years old and diagnosed with AF (with or without treatment) diagnosed by standard electrocardiogram (ECG) or Holter monitoring. At each participating site, the first 15 consecutive patients diagnosed with AF, either previously or newly identified, were required to be registered in the ReMeFa study, without considering the reason for the hospital or office visit. Since the aim of the study was to analyze the long-term outcome of patients with AF not due to transient conditions, the exclusion criteria were (thyrotoxicosis, alcohol intoxication, acute phase of myocardial infarction, pericarditis, myocarditis, electrocution, pulmonary embolism or other pulmonary diseases, electrolyte or metabolic disorder, among other conditions), heart surgery in the last three months, pulmonary vein ablation, patients with a life expectancy $<$1 year, patients unable to comply with follow-up visits, users of pacemaker or defibrillator, patients scheduled for pulmonary vein ablation, ablation of the AV node, patients in a clinical study in the field of AF in the previous three months, pregnant or lactating women, or individuals unable to understand and sign the informed consent.

At baseline demographic information on comorbidities, traditional cardiovascular risk factors, anthropometric, medical treatment, AF characteristics and quality of life was recorded employing an electronic structured and standardized clinical report format (CRF) which included the EQ-5D questionnaire as a measure of overall health status, as well as the specific Atrial Fibrillation Severity Scale (AFSS). In visits 6 $\pm$ 2 and 12 $\pm$ 3 months, we analyzed the proportion of patients with AF who went to sinus rhythm control, with symptomatic or asymptomatic AF, with antiarrhythmics, with adverse events related to treatment, with the need of cardioversion (electrical or pharmacological) or ablation, with the achievement of goals according to treatment strategy (rhythm or frequency), as well as information on the quality of life (EQ-5D questionnaires and AFSS).

At baseline, basic anthropometric measures such as weight, height, and waist circumference were registered. Weight was measured with a scale, and height was measured to the nearest 0.5 cm using a wall-mounted metric rule. Waist circumference (cm) was measured with an anthropometric tape at the minimum perimeter between the iliac crest and the lower border of the rib cage. With these measures, BMI and waist-to-height ratio (WHtR) were calculated.

The relative frequencies of nominal variables were expressed as proportions. Confidence intervals (CI) 95% for relevant relative frequencies were provided. Age is expressed as median with 25th and 75th percentiles (interquartile range) or minimum and maximum, as appropriate. The χ^2 Pearson test was used to compare proportions between two groups or to assess the homogeneity of the distribution of ratios between three or more groups. The median age between two groups was compared using the Mann-Whitney.

Multivariate analyzes were constructed by using the Cox proportional hazards model to sought for independent variables predicting 12 month all-cause CFR. Potential independent covariables were chosen to enter the model by a first-step univariate analysis if $p < 0.1$, but those variables potentially involved in outcomes prediction were also included for adjustment. Only significant predictors in the final multivariate model are described. Multivariate hazard ratios (HR) and their respective 95% confidence intervals

(95% CI) are provided. All p values calculated were two-tailed and considered significant when $p < 0.05$. SPSS v20.0 was used in all calculations in this report.

Results

We studied a total of 1201 patients with AF, among whom 1193 (99%) were evaluable for the primary objectives of ReMeFa (mean age: 67.13 years, median: 69.14 years, interquartile range: 58.24−77.62 years); 659 (55.2%) women and 534 (44.8%) men. Women were significantly older than men (69.07 vs. 64.74 years, respectively; $p < 0.001$), with 76.6% women aged >60 years, as compared with 66.5% of men ($p < 0.001$).

AF was considered symptomatic for 954 (80.4%) individuals, with 1,090 (91.4%) patients already having the diagnosis of AF before the ReMeFa registry (only 103 participants had a diagnosis of AF after the registry began). Paroxysmal AF was identified at baseline in 29.3%, persistent AF in 52.6%, and permanent AF in 18.1%. At a 6 month follow-up, 25.7% of patients were registered as having paroxysmal AF, 10.4% with persistent AF, and 63.8% with permanent AF. At a 12 month follow-up, 25.0% of survivors were registered as having paroxysmal AF, 8.7% with persistent AF, and 66.2% with permanent AF. At baseline, rhythm control as a management strategy of AF was established in 476 (39.9%) subjects, while control of frequency was offered to 717 (60.1%) patients (Table 1). Several relevant baseline differences were observed among groups of patients according to management strategy. The proportion of female gender, older age and relevant comorbidities (with exception comorbid arrhythmias other than AF) was higher in the group of frequency control. Anthropometric measures did not differ according to management groups. However, antiplatelets were prescribed to a higher proportion of patients in the rhythm-control group, as compared with those in the group of frequency control (57% vs. 35%, respectively, $p = 0.001$). Consequently, more patients in the frequency control group had prescribed oral anticoagulants (mainly vitamin K antagonists) than in the rhythm-control group (66% vs. 43%, $p = 0.001$).

At baseline, mean ± SD for height of the participants was 1.61 ± 0.11 m (1.70 meters in men, 1.55 m in women, $p < 0.001$), mean total body weight was 73.31 ± 16.66 kg (81.15 kg in men, 66.91 kg in women, $p < 0.001$), mean waist circumference was 95.47 ± 15.36 cm (99.53 cm in men, 92.16 cm in women, $p < 0.001$), mean basal WHtR was 0.591 ± 0.092 (0.586 in men, 0.595 in women, $p = 0.09$), and mean BMI was 27.97 ± 5.17 (28.07 in men, 27.88 in women, $p = 0.52$).

The 12 month all-cause case fatality rate was 8.9% ($n = 106$), with 6.0% ($n = 71$, 67.4%) corresponding to cardiovascular causes. Acute ischemic or hemorrhagic stroke occurred in 3.4% ($n = 61$) of cases during follow-up, and ischemic stroke, specifically in 2% ($n = 24$) of cases. Acute myocardial infarction occurred in only 3 (0.3%) cases. Factors significantly associated with all-cause CFR in bivariate analyses (Table 2) were AF

Table 1. Baseline characteristics of the cohort ($n = 1193$)

Baseline characteristics	Baseline atrial fibrillation type of management		p
	Rhythm control ($n = 476$)	Frequency control ($n = 717$)	
Women, %	50.0	58.7	0.003
Age, median (IQR), years	66.4 (54.9−75.66)	70.9 (61.0−78.7)	<0.001
Age >60 years, %	64.9	76.8	<0.001
Other arrhythmias, %	12.2	7.1	0.003
Diabetes mellitus, %	18.1	25.4	0.003
Hypertension, %	63.2	62.9	0.917
Congestive heart failure, %	17.9	35.2	<0.001
Heart valve disease, %	16.2	42.1	<0.001
Coronary artery disease, %	12.8	10.0	0.136
Carotid stenosis, %	0.6	0.7	46.9
Peripheral artery disease, %	3.4	4.0	0.553
Chronic kidney disease, %	3.8	5.4	0.191
History of acute ischemic stroke, %	8.0	12.0	0.026
History of transient ischemic attack, %	4.2	6.7	0.068
Thyroid endocrine disease, %	6.7	4.6	0.114
Dyslipidemia, %	32.8	31.1	0.542
Current smoking status, %	6.9	5.0	0.166
Body mass index ≥27, %	54.3	52.3	0.495
Body mass index ≥30, %	32.1	30.0	0.439
Waist-to-height ratio ≥0.60, %	45.9	43.9	0.500
Waist-to-height ratio ≥0.70, %	11.2	14.9	0.076

IQR, interquartile range.

Table 2. Bivariate analyses on baseline factors associated with 12 month all-cause case fatality rate

Baseline characteristics	Vital status at 12 month follow-up		p
	Alive (n = 1087)	Death (n = 106)	
Women, %	55.1	56.6	0.767
Age >60 years, %	71.5	78.3	0.135
AF frequency control at baseline, %	58.4	77.4	<0.001
Other arrhythmias, %	9.4	6.6	0.343
Diabetes mellitus, %	22.3	24.5	0.597
Hypertension, %	62.9	65.1	0.649
Congestive heart failure, %	27.4	37.7	0.024
Heart valve disease, %	31.3	36.8	0.244
Coronary artery disease, %	11.2	10.4	0.792
Carotid stenosis, %	0.5	2.8	0.027
Peripheral artery disease, %	3.8	3.8	0.998
Chronic kidney disease, %	4.3	9.4	0.019
History of acute ischemic stroke, %	9.9	15.1	0.097
History of transient ischemic attack, %	5.5	7.5	0.392
Thyroid endocrine disease, %	5.7	2.8	0.213
Dyslipidemia, %	32.5	23.8	0.067
Current smoking status, %	6.0	3.8	0.353
Body mass index ≥27, %	54.4	40.6	0.007
Body mass index ≥30, %	32.0	18.9	0.005
Waist-to-height ratio ≥0.60, %	54.3	65.4	0.030
Waist-to-height ratio ≥0.70, %	13.8	9.6	0.235

AF, atrial fibrillation.

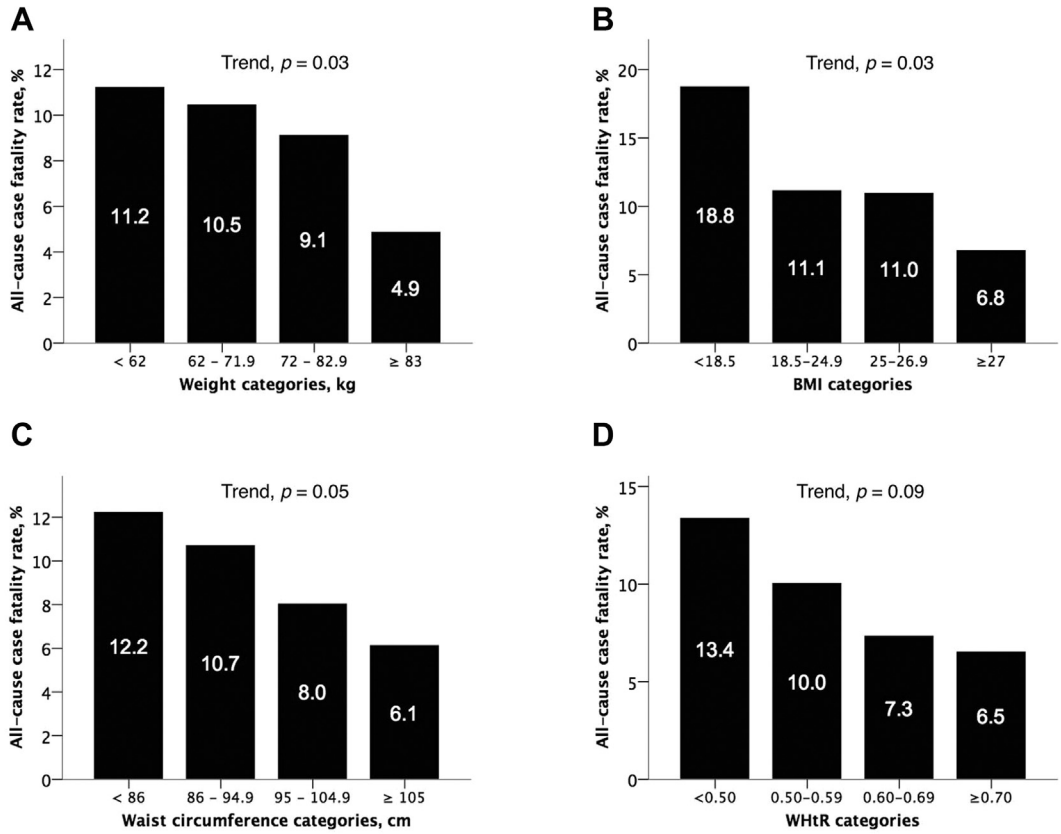

Figure 1. Twelve-month all-cause case fatality rate according to total body weight categories (A), body mass index (BMI) (B), waist circumference (C) and waist-to-height ratio (WHtR) categories (D).

frequency control at baseline, documented carotid stenosis, and chronic kidney disease. Nonetheless, increased BMI and WHtR were associated with a reduced risk of death, a paradoxical relationship that was further analyzed, so that either high total body weight, BMI categories, waist circumference or WHtR were associated with a lower-case fatality rate at 12 months of follow-up (Figure 1). Since this apparent survival advantage was significant only for BMI and body weight (as measures of total body mass instead of body adiposity), we further explored this statistical phenomenon by plotting the unadjusted hazard ratios for the probability of death at one year, according to different BMI cut-offs (Figure 2A). This analysis showed that high BMI was significantly associated with a reduced risk of death, corroborated with the survival analyses with the Kaplan-Meier method (Figure 2B). Moreover, a Cox-proportional hazards model adjusted for relevant baseline demographic and clinical covariables demonstrated that the factors independently modifying the risk of death were ascending BMI categories (HR: 0.736, 95% CI: 0.584−0.928), chronic heart failure (HR: 1.738, 95% CI: 1.127−2.680), chronic kidney disease (HR: 2.269, 95% CI: 1.162−4.429) and carotid stenosis >50% (HR: 5.342, 95% CI: 1.661−17.181) (Figure 3).

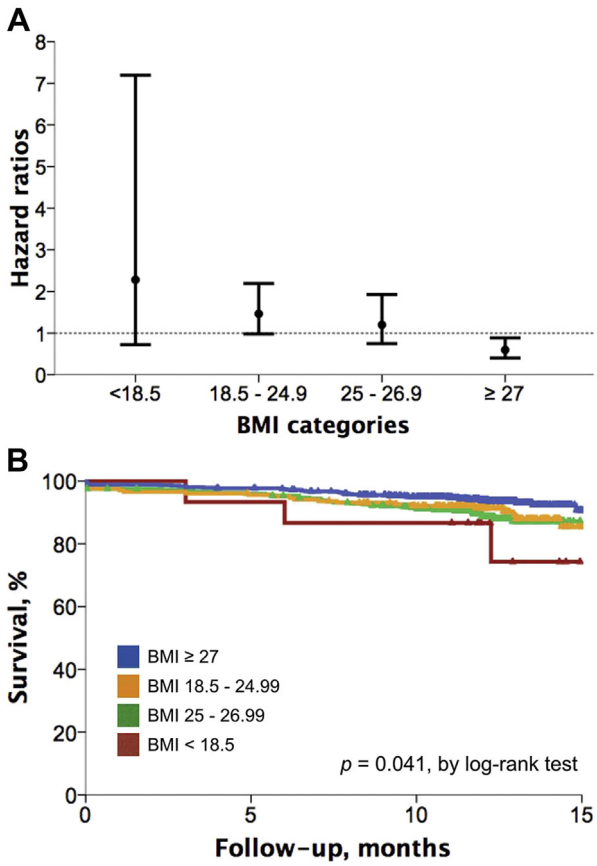

Figure 2. Analysis on the relationship of body mass index (BMI) and 12 month all-cause case fatality rate: Unadjusted hazard ratios and their respective 95% confidence intervals (error bars) for the probability of death according to different BMI cut-offs (A), Kaplan-Meier estimates on the probability of death according to different BMI categories (B). Triangles denote censored cases.

Discussion

Contrary to the primary hypothesis, in this study we identified a relationship between ''adverse'' profiles in traditional body anthropometric indices and a reduced risk of death at 12 months in a group of patients with AF. This finding can be deemed as troublesome if BMI is considered a measure of body adiposity and as a consequence, obesity index, which is not. BMI is an index of the total body mass (fat and lean) as a function of height squared (8,12−15). As such, BMI indicates either an ''adverse'' body composition profile at the expense of adiposity or a ''protectant'' characteristic related to the conservation of a certain mass, which may be critical for survival after chronic vascular and non-vascular diseases (16−20). This relationship of BMI with the high risk of acquiring vascular disease initially, and with a reduced risk of death after vascular disease occurred ultimately, has been called the obesity paradox. This phenomenon is a paradox if a high BMI is considered the pragmatic definition of obesity and a proxy for the individual nutritional state. However, from epidemiological and sanitary policy standpoints, it can be problematic considering obesity as a protecting factor. Certain body mass is necessary for survival in a diseased person, but the excess of adiposity cannot be considered as beneficial. This study adds important information to the currently widespread call

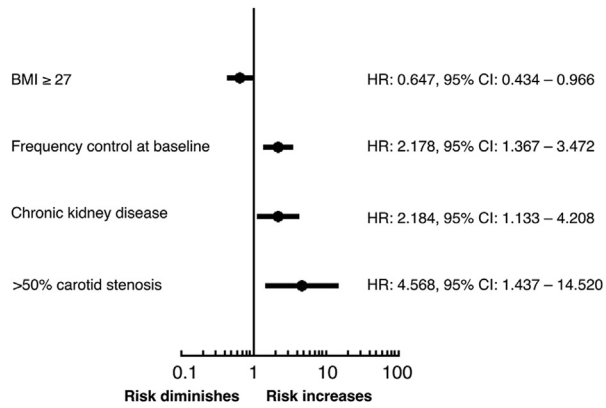

Figure 3. Forest plot on factors independently associated with 12 month all-cause case fatality rate, according to a multivariate Cox proportional hazards model adjusted for age, gender, hypertension, diabetes, dyslipidemia, coronary heart disease, smoking habit, waist circumference, waist-to-height ratio, total body weight, and frequency or rhythm control of atrial fibrillation at baseline. Body mass index (BMI) categories with hazard ratio as per BMI class: <18.5, 18.5−24.5, 24.5−29.9, 30.0−34.9, 35.0−39.9 and ≥40.0. It is shown in a log scale the hazard ratios (HR) and their respective 95% confidence intervals of statistically significant factors in the final multivariate model.

for a better clinical definition of obesity by using adequate anthropometric or body composition methods (8,12,19,20).

All-cause and cardiovascular case fatality rates were comparable with other cohorts (21−25). The risk factors associated with death in the present study have also been previously identified, including the well-known survival advantage of a high BMI in patients with AF (13,14,20). Noteworthy, chronic end-organ disease, such as heart failure and kidney disease were significantly associated with 12 month all-cause CFR, which is in accordance with previous observational studies, but different to what it is observed in randomized clinical trials, possibly due to selection criteria that apply in non-real life evidence studies (26−33). Other essential management differences have not been identified in this and previous ReMeFa analyses (10).

The main limitation of this study is related to the recruitment strategy. Although the ReMeFa investigators systematically registered the first 15 consecutive patients, it cannot be considered this as an unbiased random sampling. It is possible that obese patients at low risk (otherwise) were recruited, so that baseline characteristics or outcomes could be biased towards individuals with high BMI having other concurrent protecting characteristics. Data on physical activity and fitness would better adjust these estimations, so the lack of this information represents a limitation of the study. Nevertheless, this factor is not highly probable, as only a limited number of patients were allowed to enter the study by a relatively large number of investigators, and more importantly, these figure numbers are comparable with previous studies of patients with AF. The sample size was calculated for the primary objective of describing management strategies in this cohort, so that for the secondary analyses, limited study power may hamper the detection of other minor, but clinically relevant modifying factors of death. Although a central panel ascertained outcomes and conditions acquired during the follow-up, other previous diagnoses and antecedents may not be ultimately confirmed. Moreover, on the one hand, most patients with AF in this cohort were not newly diagnosed individuals, which may not allow for an adequate time resolution to analyze the relation between AF and clinically relevant events. On the other hand, we excluded patients under transient conditions that might lead to AF. Therefore, we cannot discard that our exclusion criteria might bias the analysis of relatively healthy people. The present report should be considered a hypothesis-generating study that warrants the future by searching for better anthropometric measures that can adequately indicate obesity's fundamental characteristic: the excess of body adiposity.

These findings suggest that certain body mass is necessary for survival after the cardiovascular disease has taken place, and other important baseline conditions such as carotid stenosis, chronic kidney disease and heart failure (among possibly several other factors not here detected) are the main determinants for one-year survival in AF patients (34,35). Among them, control of reversible baseline comorbidities appears to be the most critical determinant for survival. Even when this analysis is consistent with an apparent paradoxical relation of BMI and WHtR with CFR in patients with AF, since these anthropometric measures are not direct and perfect indicators of adiposity, we cannot conclude that obesity is protective. On the contrary, we should emphasize body weight control and obesity prevention to promote a healthier lifestyle (36−38).

Conclusion

All-cause CFR at one year of follow-up in patients with AF is inversely associated with BMI and directly associated with chronic kidney disease, carotid stenosis, and chronic heart failure in this cohort of Mexican patients with AF. The causes and implications of this apparent obesity paradox in participants with AF should be addressed in the future.

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