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ORIGINAL RESEARCH

Impact of Weight Gain on Cardiovascular Outcomes in Patients With Atrial Fibrillation

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BACKGROUND: The long-term impact of weight gain (WG) on cardiovascular outcomes among patients with atrial fibrillation (AF) is unclear.

METHODS AND RESULTS: We studied 62 871 (mean age, 72±12, 43% women) adult patients with AF evaluated at the University of Pittsburgh Medical Center between January 1, 2010, and May 13, 2021. Serial body mass index, risk factors, comorbidities, and subsequent death and hospitalization were ascertained and stratified according to percentage WG (≥0% to <5%, ≥5% to <10%, and ≥10%). Over 4.9±3.19 years of follow-up, 27 114 (43%) patients gained weight (61%, ≥0% to <5%; 23%, ≥5% to <10%; 16%, ≥10%). Patients with progressive WG were incrementally younger (P<0.001) women (40%, 42%, and 47%) with lower median household income (P=0.002) and active smoking (8%, 13% and 13%), and they were less likely to be on a non–vitamin K oral anticoagulant (39%, 37%, and 32%). WG was incrementally associated with a significant increase in risk of hospitalization for AF (≥10% WG; hazard ratio [HR], 1.2 [95% CI, 1.2–1.3]; P<0.0001), heart failure (≥10% WG; HR, 1.44 [95% CI, 1.3–1.6]; P<0.001; ≥5% to <10% WG; HR, 1.17 [95% CI, 1.1–1.2]; P<0.001), myocardial infarction (≥10% WG; HR, 1.2 [95% CI, 1.3–1.6]; P<0.001) and all-cause stroke (4.2%, 4.3%, and 5.6%) despite significantly lower mean $CHADS_2Vasc$ score (2.9±1.7, 2.7±1.6, and 2.7±1.7). Patients with more WG were significantly more likely to receive cardiac and electrophysiologic interventions.

CONCLUSIONS: Among patients with AF, WG is incrementally associated with increased hospitalization for cardiovascular causes, particularly heart failure, stroke, myocardial infarction, and AF.

Key Words: atrial fibrillation ■ obesity ■ risk factors

The prevalence of atrial fibrillation (AF) and obesity continues to increase.[1] These 2 chronic diseases are complexly interrelated both in pathophysiology and in clinical outcomes. Obesity, as measured by elevated body mass index (BMI), has been associated in multiple prior observational studies with future occurrence of incident AF.[2] At the same time, intentional weight loss has been associated with decreased AF frequency.[3] Based on this, weight loss/control is an integral part of scientific AF risk factor management guidelines.[4] Patients with AF often receive advice regarding harmful effects of weight gain (WG) as part of integrated care, although this aspect of AF management is currently underrecognized and underused. However, among patients with established AF, the long-term impact of WG on cardiovascular outcomes has not been investigated in any major real-world cohort. Additionally, the dose dependency of WG on heart failure (HF), myocardial infarction (MI), stroke, and AF hospitalizations and all-cause death among patients with AF is not defined. Data clarifying the association of incremental WG with clinical outcomes in patients with

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CLINICAL PERSPECTIVE

What Is New?

- Our study demonstrates that among patients with prevalent atrial fibrillation, progressive weight gain was incrementally associated with increased hospitalization for cardiovascular causes, not only for atrial fibrillation but heart failure, stroke, and myocardial infarction.

What Are the Clinical Implications?

- Patients with the most weight gain have a unique demographic and risk profile and experience significantly increased cardiac and electrophysiologic interventions.

Nonstandard Abbreviations and Acronyms

WG	weight gain

established AF would encourage focus on weight loss as an essential part of management of these patients. Therefore, our study has the following objectives: (1) to characterize the clinical phenotype of patients with prevalent AF who gain weight; (2) to investigate the impact of WG on cardiovascular outcomes in patients with established AF; and (3) to understand use of cardiovascular interventions among various WG strata of patients with prevalent AF.

METHODS

Study Population

This was a retrospective observational cohort study that included patients aged >18 years who had at least 2 outpatient visits with either internal medicine, family medicine, or cardiology clinics of the University of Pittsburgh Medical Center with an associated diagnosis of AF. The diagnosis of AF was based on the presence of *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes (*ICD-9*: 427.31, 427.32; *ICD-10*: I48.0, I48.1, I48.2, I48.91, I48.3, I48.4, I48.92). These patients were evaluated between January 1, 2001, to May 13, 2021, and the study was approved by the University of Pittsburgh Institutional Review Board. The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to the retrospective nature of the study, informed consent was not required.

Patient Characteristics

The University of Pittsburgh Medical Center is an integrated insurance and provider system with >40 academic, community, and specialty hospitals. The hospital system's wide electronic health record data are aggregated and harmonized with administrative, financial, and other publicly available data in its Clinical Data Warehouse; and the Data and Analytics Program was used to obtain the clinical parameters including age at presentation; sex; race; cardiovascular risk factors, including presence of smoking history, hypertension, diabetes, coronary artery disease, congestive HF, mitral valve disease, hyperlipidemia, and vascular history including prior history of deep vein thrombosis and major bleeding; neurological history including prior ischemic or hemorrhagic stroke and transient ischemic attack; prior ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation); and prior cardiac arrest. Major comorbidities evaluated included chronic obstructive pulmonary disease, prior history of cancer, obstructive sleep apnea, chronic kidney disease, and liver disease. Current Procedural Terminology codes were used to ascertain prior automatic implantable cardioverter-defibrillator implantation, permanent pacemaker implantation, pulmonary vein ablation, atrioventricular node ablation, cardioversion, and loop monitor implants, along with cardiac interventions including percutaneous coronary intervention, coronary artery bypass grafting, maze, or mitral valve surgery during follow up. Medication use at baseline was evaluated including use of antiarrhythmic agents, antiplatelets, anticoagulants, and rate control medications. BMI was calculated from height and weight obtained at the initial baseline and last follow-up visit using the formula BMI = (weight[kg]/height[m]^2). Patients who were underweight (BMI <18.5 at baseline) were excluded to avoid confounding the impact of WG upon outcomes.[5] The initial and final height and weight and subsequent BMI were used to calculate percentage WG for the study population with the cohort stratified according to the magnitude of WG (≥0% to <5%, ≥5% to <10%, and ≥10%) for the purpose of analysis.

Outcome

The primary outcome of interest included hospitalization for cardiovascular causes, MI, AF, HF, stroke, or major bleeding A hospitalization was attributed to the primary outcome if the corresponding *ICD-9/10* code was listed as 1 of the top 3 diagnoses (primary, principal, or secondary) during an inpatient admission. Cardiac interventions performed during follow-up were evaluated including electrophysiologic interventions (device therapy, ablation, cardioversions) and percutaneous coronary interventions. The secondary outcome

Table 1. Baseline Demographic and Cardiovascular Characteristics of the Study Population Stratified by Weight Change

Clinical characteristics	Total	WG ≥0% to <5%	WG ≥5% to <10%	WG ≥10%	*P* value
N	27 114	16 485 (61%)	6375 (23%)	4254 (16%)	
Age, y(range)	69.7±12.7 (19.1–102.9)	71.0±12.4 (19.1–102.9)	68.7±12.6 (18.2–98.8)	66.1±13.5 (18.5–101.2)	<0.001
Sex, female, n (%)	11 312 (41.72)	6635 (40.25)	2679 (42.02)	1998 (46.97)	<0.001
Baseline BMI	30.2±6.86	30.4±6.83	30.2±6.86	29.6±6.95	0.001
BMI categories, n (%)					
Normal weight (18.5–24.9)	6092 (22.47)	3454 (20.95)	1423 (22.32)	1215 (28.56)	<0.001
Overweight (25–29.9)	9051 (33.38)	5579 (33.83)	2153 (33.77)	1319 (31.01)	
Obese (30–39.9)	9593 (35.38)	5999 (36.39)	2228 (34.95)	1366 (32.11)	
Morbid obesity (≥40)	2378 (8.77)	1453 (8.81)	571 (8.96)	354 (8.32)	
Final BMI	32.0±7.37	31.1±6.98	32.5±7.37	34.5±8.17	0.001
Median household income	52 403±16 786	52 585±16 778	52 479±16 971	51 578±16 515	0.002
Type of insurance, n (%)					
University of Pittsburgh Medical Center Health Plan	7872 (29.03)	4736 (28.73)	1836 (28.80)	1300 (30.56)	0.057
Commercial	8925 (32.92)	5233 (31.74)	2187 (34.31)	1505 (35.38)	<0.001
Medicare	17 782 (65.58)	11 297 (68.53)	4048 (63.50)	2437 (57.29)	<0.001
Medicaid	2623 (9.67)	1327 (8.05)	643 (10.09)	653 (15.35)	<0.001
Race, n (%)					
White	25 753 (94.98)	15 727 (95.40)	6049 (94.89)	3977 (93.49)	<0.001
Black	1026 (3.78)	554 (3.36)	243 (3.81)	229 (5.38)	
Other	335 (1.24)	204 (1.24)	83 (1.30)	48 (1.13)	
Cancer history, n (%)	3722 (13.73)	2314 (14.04)	844 (13.24)	564 (13.26)	0.182
$CHADS_2Vasc$	2.83±1.67	2.91±1.67	2.74±1.65	2.66±1.66	<0.001
Tobacco status, n (%)					
Never	12 322 (45.45)	7595 (46.07)	2914 (45.71)	1813 (42.62)	<0.001
Current	2575 (9.50)	1368 (8.30)	642 (10.07)	565 (13.28)	
Previous	11 452 (42.24)	7064 (42.85)	2633 (41.30)	1755 (41.26)	
Other	765 (2.82)	458 (2.78)	186 (2.92)	121 (2.84)	
Cardiac history, n (%)					
Hypertension	17 796 (65.63	10 991 (66.67)	4109 (64.45)	2696 (63.38)	<0.001
Diabetes	6145 (22.66)	3804 (23.08)	1442 (22.62)	899 (21.13)	0.025
Coronary artery disease	8352 (30.80)	5249 (31.84)	1887 (29.60)	1216 (28.58)	<0.001
Congestive heart failure	6150 (22.68)	3632 (22.03)	1439 (22.57)	1079 (25.36)	<0.001
Hyperlipidemia	15 975 (58.92)	9990 (60.60)	3707 (58.15)	2278 (53.55)	<0.001
Mitral stenosis	2346 (8.65)	1461 (8.86)	530 (8.31)	355 (8.35)	0.308
Pulmonary hypertension	1010 (3.73)	624 (3.79)	201 (3.15)	185 (4.35)	0.005
Vascular history, n (%)					
Deep vein thrombosis	786 (2.90)	460 (2.79)	197 (3.09)	129 (3.03)	0.409
Pulmonary embolism	818 (3.02)	482 (2.92)	189 (2.96)	147 (3.46)	0.188
Peripheral vascular disease	1653 (6.10)	1045 (6.34)	378 (5.93)	230 (5.41)	0.063
Major bleeding	3435 (12.67)	2083 (12.64)	818 (12.83)	534 (12.55)	0.896
Neurological history, n (%)					
Ischemic stroke	2649 (9.77)	1643 (9.97)	596 (9.35)	410 (9.64)	0.352
Hemorrhagic stroke	173 (0.64)	98 (0.59)	47 (0.74)	28 (0.66)	0.470
Transient ischemic attack	945 (3.49)	592 (3.59)	219 (3.44)	134 (3.15)	0.365
Echocardiographic findings	10 700	6236	2614	1850	
Ejection fraction	52.1±11.3	52.5±10.9	51.8±11.5	50.9±12.4	<0.001
Ejection fraction ≤35, n (%)	939 (3.46)	487 (2.95)	239 (3.75)	213 (5.01)	<0.001

(*Continued*)

Table 1. Continued

Clinical characteristics	Total	WG ≥0% to <5%	WG ≥5% to <10%	WG ≥10%	*P* value
Left atrial diameter	4.10±0.76	4.11±0.76	4.10±0.74	4.09±0.77	0.762
Left ventricular septal thickness	1.14±0.24	1.15±0.24	1.14±0.24	1.14±0.23	0.032
Left ventricular hypertrophy, n (%)	4106 (15.14)	2416 (14.66)	963 (15.11)	727 (17.09)	0.211
Arrhythmic history, n (%)					
Ventricular tachycardia / ventricular fibrillation	822 (3.03)	458 (2.78)	215 (3.37)	149 (3.50)	0.009
Cardiac arrest	104 (0.38)	49 (0.30)	27 (0.42)	28 (0.66)	0.003
Cardiac interventions, n (%)					
Prior implantable cardioverter-defibrillator implant	510 (1.88)	295 (1.79)	125 (1.96)	90 (2.12)	0.327
Prior pacemaker implant	976 (3.60)	622 (3.77)	222 (3.48)	132 (3.10)	0.095
Prior pulmonary vein isolation ablation	107 (0.39)	77 (0.47)	17 (0.27)	13 (0.31)	0.057
Prior atrioventricular node ablation	260 (0.96)	137 (0.83)	63 (0.99)	60 (1.41)	0.002
Prior cardioversion	2812 (10.37)	1604 (9.73)	730 (11.45)	478 (11.24)	<0.001
Prior loop monitor implant	97 (0.36)	64 (0.39)	18 (0.28)	15 (0.35)	0.485
Prior percutaneous coronary intervention	2058 (7.59)	1268 (7.69)	474 (7.44)	316 (7.43)	0.734
Prior coronary artery bypass grafting	1179 (4.35)	671 (4.07)	303 (4.75)	205 (4.82)	0.020
Prior maze surgery	103 (0.38)	53 (0.32)	29 (0.45)	21 (0.49)	0.143
Prior mitral valve surgery	457 (1.69)	263 (1.60)	103 (1.62)	91 (2.14)	0.043

BMI indicates body mass index; and WG, weight gain.

of interest was all-cause death, which was ascertained by review of the Social Security Death Index and enriched by electronic health record data input (hospitalization data or office visit) aggregated in the Clinical Data Warehouse.

Statistical Analysis

For baseline characteristics, continuous variables are presented as mean±SD, or median and interquartile range, and compared between groups using the Student *t* test or nonparametric Mann–Whitney test as appropriate. Categorical variables are presented as frequencies and percentages and compared using the χ^2 test. Baseline demographic and cardiovascular characteristics of the study population were stratified according to weight categories (gain [≥0% to <5%, ≥5% to <10%, ≥10%]) with stable weight ([≥0% to <5%]) category used as reference. Patients with missing or nonvalid value for weight or BMI were excluded from the analysis. Kaplan–Meier survival analysis was used to evaluate hospitalization-free survival for each cardiovascular outcome. A Cox proportional hazard model was used to examine independent predictors of primary and secondary outcome in patients using a stepwise selection approach adjusting for baseline BMI along with all pertinent clinical covariates. Fine and Gray competing risk regression was used for the hospitalization outcomes allowing for competing death. Any significant 2-way interaction of WG groups with other covariates was tested and reported, and α of 0.05 was used to confirm significance. We additionally performed propensity score analyses (sensitivity) using greedy nearest neighbor caliper matching, with calipers of width setting at 0.2 of SD matching WG (≥10%) to the other 2 groups with subsequent survival and Cox regression analysis on the matched sample. The variables included age, sex, $CHAD_2Vasc$, race, smoking history, prior coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), prior implantable cardioverter-defibrillator implantation, prior mitral valve disease, prior major bleeding, hyperlipidemia, prior stroke, prior ventricular tachycardia/ventricular fibrillation, prior cardiac arrest, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, history of cancer, prior class 1 or class 3 antiarrhythmic drug use, prior stain use, and prior anticoagulation. SAS version 9.4 software (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS

Study Population

Nearly half of the AF population (n=27 114 [43%]) gained weight during the follow-up period and constituted the study cohort, with 16% gaining >10%. The demographic and clinical characteristics stratified by the percentage WG are depicted in Table 1. Patients with more WG were incrementally younger (*P*<0.001) women (40%, 42%, and 47%) with lower median household income (*P*=0.002) and more Medicaid use (8%, 10%, and 15%), Although they had lower hypertension, diabetes, and coronary artery disease, patients with more WG had significantly higher prevalence of HF (Table 1). Echocardiographic data were available for nearly half the cohort and patients with ≥10% WG have significantly lower left ventricular function on echocardiography (50.9±12.4; 5% with <35% ejection fraction; *P*<0.001), and more ventricular tachycardia/ventricular fibrillation (2.8%, 3.4%, and 3.5%). Table 2 shows the comorbid burden with significantly higher levels of active smoking (8%, 13%, and 13%) and liver disease. They were also less likely to be on a non–vitamin K oral anticoagulant (39%, 37%, and 32%) with higher class 3 antiarrhythmic drug use (16%, 18%, and 20%; Table 2).

Outcomes

Hospitalization

Table 3 details the long-term clinical outcomes stratified by the degree of WG among patients with AF. Over 4.9±3.19 years of follow up, patients with more WG experienced significantly higher burden of cardiac, HF, AF (all *P*<0.001), major bleed (*P*=0.018) and all-cause stroke hospitalization (4.2%, 4.3%, and 5.6%; *P*<0.001) despite significantly lower mean $CHADS_2Vasc$ score (2.9±1.7, 2.7±1.6, and 2.7±1.7). Kaplan–Meier survival analysis is shown in the Figure for outcome of AF and HF hospitalization. Comprehensive covariate baseline BMI, age, sex, non-White race, history of smoking, prior coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting),

Table 2. Comorbidity Burden and Medication Use of the Study Population Stratified by Weight Change During Follow-Up

Clinical characteristics	Total	WG ≥0% to <5%	WG ≥5% to <10%	WG ≥10%	*P* value
No.	27 114	16 485	6375	4254	
Current smoker, n (%)	2575 (9.50)	1368 (8.30)	642 (10.07)	565 (13.28)	<0.001
Chronic obstructive pulmonary disease, n (%)	3809 (14.05)	2286 (13.87)	878 (13.77)	645 (15.16)	0.074
Obstructive sleep apnea, n (%)	3882 (14.32)	2394 (14.52)	908 (14.24)	580 (13.63)	0.331
Chronic kidney disease, n (%)	1991 (7.34)	1285 (7.79)	444 (6.96)	262 (6.16)	<0.001
End-stage renal disease, n (%)	265 (0.98)	157 (0.95)	57 (0.89)	51 (1.20)	0.257
Liver disease, n (%)	1417 (5.23)	796 (4.83)	334 (5.24)	287 (6.75)	<0.001
Elixhauser AHRQ score	1.87±6.39	1.81±6.27	1.82±6.39	2.18±6.83	0.003
Medications	**Overall**	**WG ≥0% to <5%**	**WG ≥5% to <10%**	**WG ≥10%**	***P* value**
No.	27 114	16 485	6375	4254	
Aspirin, n (%)	15 298 (56.42)	9317 (56.52)	3648 (57.22)	2333 (54.84)	0.049
Warfarin, n (%)	7494 (27.64)	4398 (26.68)	1785 (28.00)	1311 (30.82)	<0.001
DOAC, n (%)	10 204 (37.63)	6496 (39.41)	2350 (36.86)	1358 (31.92)	<0.001
Antiplatelet, n (%)	2949 (10.88)	1771 (10.74)	708 (11.11)	470 (11.05)	0.678
Class 1 AAD, n (%)	1056 (3.89)	646 (3.92)	266 (4.17)	144 (3.39)	0.117
Class 3 AAD, n (%)	4720 (17.41)	2686 (16.29)	1173 (18.40)	861 (20.24)	<0.001
Calcium channel blocker, n (%)	9258 (34.14)	5666 (34.37)	2193 (34.40)	1399 (32.89)	0.169
β Blocker	18 492 (68.20)	11 227 (68.10)	4350 (68.24)	2915 (68.52)	0.870
Statin, n (%)	15 122 (55.77)	9467 (57.43)	3481 (54.60)	2174 (51.10)	<0.001
Rate control (digoxin), n (%)	2978 (10.98)	1634 (9.91)	724 (11.36)	620 (14.57)	<0.001
ACEI/ARB/ARNI	13 764 (50.76)	8503 (51.58)	3148 (49.38)	2113 (49.67)	0.004
ACEI	9305 (34.32)	5666 (34.37)	2138 (33.54)	1501 (35.28)	0.173
ARB	4904 (18.09)	3092 (18.76)	1119 (17.55)	693 (16.29)	<0.001
ARNI	146 (0.54)	99 (0.60)	33 (0.52)	14 (0.33)	0.094

AAD indicates antiarrhythmic drug; ACEI, angiotensin-converting enzyme inhibitor; AHRQ, Agency for Healthcare Research and Quality; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; DOAC, direct-acting oral anticoagulant; and WG, weight gain.

Table 3. Long-Term Outcomes Including Cardiovascular Hospitalization, Cardiac Interventions, and All-Cause Death Among the Study Population

Outcomes	Total	WG ≥0% to <5%	WG ≥5% to <10%	WG ≥10%	*P* value
No.	27 114	16 485	6375	4254	
Age, y (last follow up)	72.8±12.4	73.7±12.2	72.3±12.3	70.3±13.1	<0.001
Duration of follow-up, y	4.67±3.08	4.38±3.09	4.96±3.05	5.38±2.93	<0.001
Hospitalization, n (%)					
Cardiac	11 131 (41.05)	6259 (37.97)	2735 (42.90)	2137 (50.24)	<0.001
Heart failure	4480 (16.52)	2427 (14.72)	1117 (17.52)	936 (22.00)	<0.001
Atrial fibrillation	6492 (23.94)	3640 (22.08)	1576 (24.72)	1276 (30.00)	<0.001
Myocardial infarction	1332 (4.91)	756 (4.59)	324 (5.08)	252 (5.92)	0.001
All-cause stroke	1201 (4.43)	688 (4.17)	274 (4.30)	239 (5.62)	<0.001
Hemorrhagic stroke	313 (1.15)	191 (1.16)	66 (1.04)	56 (1.32)	0.412
Ischemic stroke	781 (2.88)	443 (2.69)	184 (2.89)	154 (3.62)	0.005
Transient ischemic attack	259 (0.96)	143 (0.87)	64 (1.00)	52 (1.22)	0.095
Bleed	1352 (4.99)	781 (4.74)	325 (5.10)	246 (5.78)	0.018
Cardiac interventions, n (%)					
Percutaneous coronary intervention	1019 (3.76)	567 (3.44)	264 (4.14)	188 (4.42)	0.002
Pacemaker implant	902 (3.33)	536 (3.25)	213 (3.34)	153 (3.60)	0.533
Implantable cardioverter-defibrillator implant	368 (1.36)	180 (1.09)	101 (1.58)	87 (2.05)	<0.001
Pulmonary vein isolation ablation	1637 (6.04)	938 (5.69)	435 (6.82)	264 (6.21)	0.005
Atrioventricular node ablation	830 (3.06)	463 (2.81)	205 (3.22)	162 (3.81)	0.002
Cardioversion	3398 (12.53)	1960 (11.89)	831 (13.04)	607 (14.27)	<0.001
Loop monitor implant	101 (0.37)	57 (0.35)	27 (0.42)	17 (0.40)	0.654
Left ventricular assist device/transplant	76 (0.28)	35 (0.21)	19 (0.30)	22 (0.52)	0.004
Death	5561 (20.51)	3449 (20.92)	1232 (19.33)	880 (20.69)	0.026

WG weight gain.

prior defibrillator implantation, HF, peripheral vascular disease, diabetes, coronary artery disease, mitral valve disorder, hypertension, prior major bleed, hyperlipidemia, prior stroke, prior ventricular tachycardia/ventricular fibrillation, prior resuscitated cardiac arrest, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, history of cancer, antiarrhythmic drug use, statin use, and anticoagulation use adjusted Cox proportional hazard model is reported in Table 4. After multivariable adjustment, WG was incrementally associated with significant increase in risk of hospitalization for AF (≥10% WG hazard ratio [HR], 1.2 [95% CI, 1.2–1.3]; *P*<0.0001), HF (≥10% WG HR, 1.5 [95% CI, 1.3–1.6]; *P*<0.001), MI (≥10% WG HR, 1.2 [95% CI, 1–1.4]; *P*=0.019), all-cause stroke (≥10% WG HR, 1.3 [95% CI, 1.1–1.5]; *P*=0.007), and major bleeding (≥10% WG HR, 1.2 [95% CI, 1–1.4]; *P*<0.039). Additionally, patients with 5% to 10% WG also experienced increased cardiac and AF (HR, 1.2 [95% CI, 1.1–1.3]; *P*<0.001) hospitalization and increased HF hospitalization in those without prior HF (interaction analysis Tables S1 and S2). No significant interaction of WG category with baseline BMI, age, diabetes, or sex was noted (Tables S2 and S3).

Cardiac Interventions

Patients with more WG were significantly more likely to receive cardiac (percutaneous coronary intervention [*P*=0.002] and left ventricular assist device/cardiac transplant [*P*=0.004]), and electrophysiological (pulmonary vein ablation [*P*=0.005], atrioventricular node ablation [*P*=0.002], cardioversions [*P*<0.001], and automatic implantable cardioverter-defibrillator implant [*P*<0.001]) interventions during the follow-up period (Table 3).

Death

Patients with moderate WG had the least all-cause death (21%, 19%, and 21%; *P*=0.026). This (5%–10%) WG strata was associated with the lowest mortality risk (HR, 0.92 [95% CI, 0.9–1.0]; *P*<0.012) in adjusted analysis (Table S4). Age, baseline BMI strata, and presence of HF demonstrated significant interaction modifying the association of WG with all-cause death (Table S5).

No significant interaction was noted between WG groups and initial specialty of evaluation (cardiology or other; Table S6). Results of the propensity score match analysis are presented in Tables S7 and S8 along with

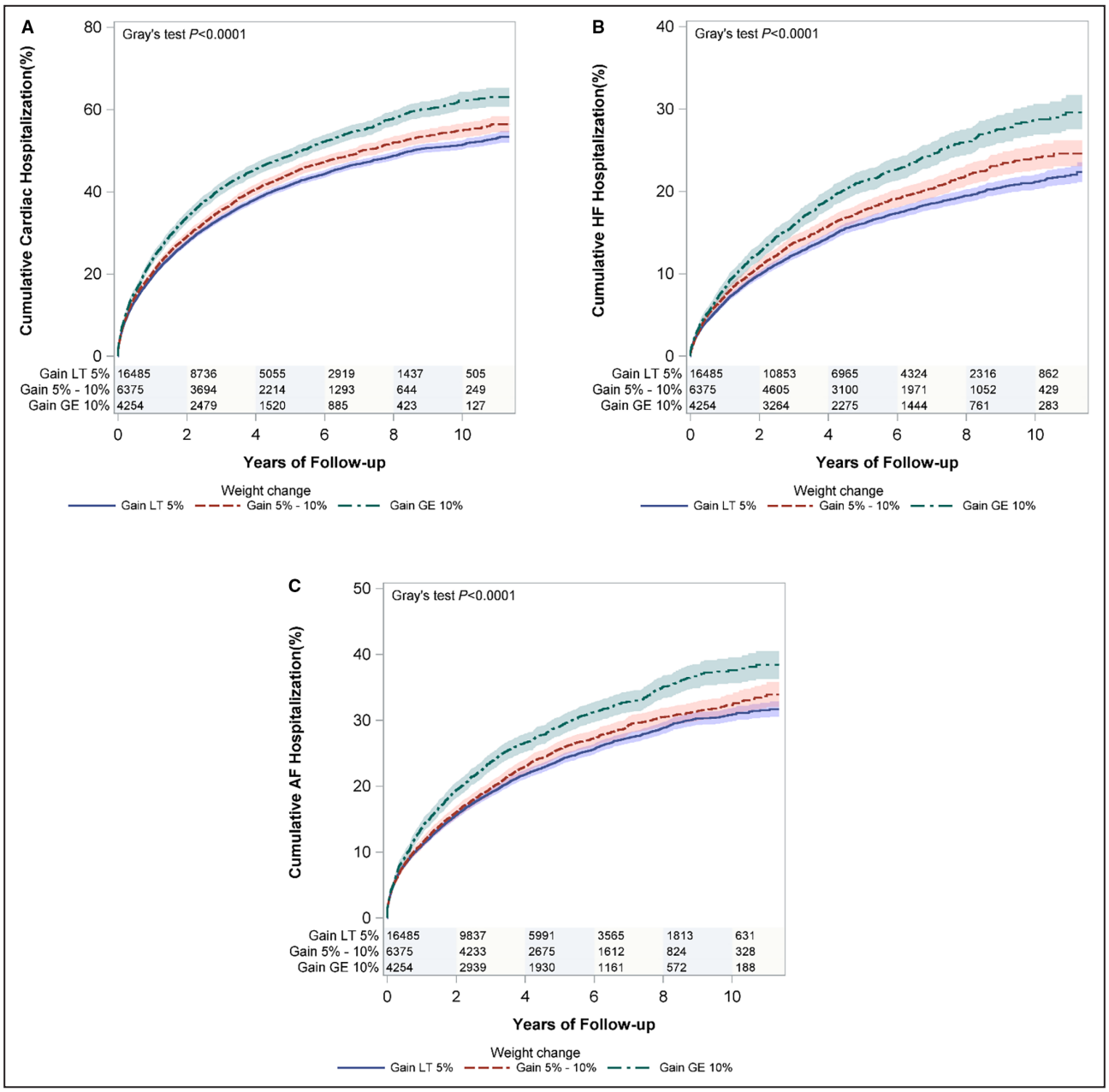

Figure. Kaplan–Meier analysis depicting (A) cardiovascular, (B) HF, and (C) AF hospitalization over the duration of follow up according to the weight gain strata.
AF indicates atrial fibrillation; GE, greater than; HF, heart failure; and LT, less than.

Figure S1A through S1C that were consistent with the primary data analysis. Sensitivity analysis performed by exclusion of patients with valvular AF are presented in Table S9 and remained consistent with overall cohort analysis.

DISCUSSION

Data from our large real-world observational cohort lead to 3 important conclusions. First, obesity is a notable comorbidity in many patients with AF at initial evaluation, and these patients experience significant WG over 5 years of follow-up. Second, a unique demographic, comorbidity, and socioeconomic profile characterizes those who gain the most weight. Finally, progressive WG is incrementally associated with worse clinical outcomes of AF, HF, stroke, MI, and bleeding-related hospitalizations along with significant increase in cardiovascular interventions and electrophysiological procedures.

Obesity represents the second-highest population-attributable risk for AF,[6] particularly notable among

Table 4. Multivariable Regression Hazard Estimates for Incremental WG and Cardiovascular Outcomes

Clinical variable	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
	WG >10%			WG 5%—10%		
Hospitalization						
Cardiac	1.27	1.21–1.34	<0.001	1.08	1.03–1.13	<0.001
HF	1.46	1.35–1.58	<0.001	1.17	1.09–1.26	<0.001
AF	1.23	1.15–1.31	<0.001	1.04	0.98–1.10	0.248
MI	1.19	1.03–1.38	0.019	1.05	0.92–1.20	0.435
All-cause stroke	1.26	1.07–1.48	0.007	0.99	0.85–1.15	0.859
Major bleeding	1.17	1.01–1.35	0.039	1.04	0.91–1.18	0.593

Model covariates: body mass index, age, sex, non-White race, smoking history, prior percutaneous coronary intervention, prior coronary artery bypass grafting, presence of implantable cardioverter-defibrillator, congestive heart failure, peripheral vascular disease, hypertension, diabetes, coronary artery disease, mitral valve disorder, prior major bleed, hyperlipidemia, prior stroke, prior ventricular tachycardia/ventricular fibrillation, prior cardiac arrest, chronic kidney disease, chronic pulmonary disease, liver disease, prior cancer, antiarrhythmic drug use, statin use, and anticoagulation use.

AF indicates atrial fibrillation; HF, heart failure; MI, myocardial infarction; and WG, weight gain.

younger patients with AF. State-, age-, and sex-specific obesity data graphs from the Centers for Disease Control and Prevention for the year 2021[7] show an obesity prevalence >30%, which is consistent with the proportion of AF patients who are obese or morbidly obese (29%) seen in our cohort. Also, from 1999 to 2000 through 2017 to March 2020, US obesity prevalence increased from 30.5% to 41.9%,[7] likely contributing to the AF epidemic, particularly in younger patients with AF. Furthermore, nearly 40% of our study cohort gained >5% of body weight over a mean follow-up of 5 years, which is more than anticipated. Prior cohort studies indicate that adults gain weight at a rate of about 0.7 to 1 pound/year (≈1% of body weight)[8,9] with weight growth curves reported to plateau around the seventh decade[10] (our cohort age, 72±12 years). In a large cohort,[6] >10%, 5% to 10%, and 0% to 5% of WG over a decade was noted for 33%, 21%, and 9% of the population, respectively, whereas 26%, 15%, and 7% of our patients with AF gained that amount only over 5 years.

Analysis of the possible reasons for this WG points toward younger age, female sex, non-White race, lower socioeconomic situation, and Medicaid insurance usage as being notable demographic and social factors associated with the patients with AF who gain the most weight. This is consistent with the Centers for Disease Control and Prevention data that obesity affects some groups more than others,[11] and age, ethnicity, and income/educational level play an important role. Identifying and addressing the social determinants that drive the complex interplay between WG and AF is a necessary next step and an opportunity to reduce AF complications.[12] These patients not only have increased antiarrhythmic drug use but also have a more severe clinical picture, with increased prevalence of HF, left ventricular dysfunction, and ventricular arrhythmias.

A number of studies previously report on increased AF incidence with increasing BMI categories.[2] More recently, analysis of updated measures of BMI[13] have hinted at more AF incidence, while smaller studies suggest more recurrence in those who gain >2 BMI units of weight[14] or with BMI fluctuations.[3] Our study uniquely demonstrates that among patients with prevalent AF, progressive WG was incrementally associated with increased hospitalization for cardiovascular causes not only for AF but HF, stroke, and MI, along with a significant increase in downstream cardiac interventions. By focusing the care of patients with AF on risk factor management including integration of weight loss strategies into comprehensive AF clinics, alongside evaluation of the social determinants of AF, we can possibly improve not only AF but global cardiovascular outcomes in patients with prevalent AF. Social determinants of heath include the domains of education, food insecurity, economic stability, neighborhood or social cohesion, health care system, and social context that clearly impact the risk of WG.[15] These are now also increasingly realized to affect outcomes among patients with AF given shared risk milieu and should become the focus of clinical management and adverse outcome prevention.[11]

Our study has significant limitations. Although a large cohort, these are retrospective cohort data with their inherent selection and other biases as they use integrated administrative and electronic health record information. We did not have information on surgical weight reduction therapy that some patients who are morbidly obese may have undergone. We also did not evaluate alcohol use and therapy for sleep apnea as potential confounders in our associations. However, adjustment for all the pertinent clinical covariates provides robustness to the results from this large real-world cohort.

In conclusion, in a real-world contemporary cohort of patients with AF evaluated in a large health care system, WG was incrementally associated with increased hospitalization for cardiovascular causes, particularly HF,

stroke, MI, and AF. These patients have a unique demographic and risk profile and experience significantly increased cardiac and electrophysiology interventions.

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Supplemental Material

Data S1

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