Association of Body Mass Index, Diabetes, Hypertension, and Blood Pressure Levels with Risk of Permanent Atrial Fibrillation

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BACKGROUND: After an initial episode of atrial fibrillation (AF), AF may recur and become permanent. AF progression is associated with higher morbidity and mortality. Understanding the risk factors for permanent AF could help identify people who would benefit most from interventions.

OBJECTIVE: To determine whether body mass index (BMI), diabetes, hypertension, and blood pressure levels are associated with permanent AF among people whose initial AF episode terminated.

DESIGN: Population-based inception cohort study.

PARTICIPANTS: Enrollees in Group Health, an integrated health care system, aged 30–84 with newly diagnosed AF in 2001–2004, whose initial AF terminated within 6 months and who had at least 6 months of subsequent follow-up ($N=1,385$).

MAIN MEASURES: Clinical characteristics were determined from medical records. Permanent AF was determined from medical records and ECG and administrative databases. Permanent AF was defined as AF present on two separate occasions 6–36 months apart, without any documented sinus rhythm between the two occasions. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs).

KEY RESULTS: Five-year cumulative incidence of permanent AF was 24 %. Compared with normal BMI (18.5–24.9 kg/m²), BMI levels of 25.0–29.9 (overweight), 30.0–34.9 (obese 1), 35.0–39.9 (obese 2), and ≥ 40.0 kg/m² (obese 3) were associated with HRs of permanent AF of 1.26 (95 % CI: 0.92, 1.72); 1.35 (0.96, 1.91); 1.50 (0.97, 2.33); and 1.79 (1.13, 2.84), adjusted for age, sex, diabetes, hypertension, blood pressure, coronary heart disease, valvular heart disease, heart

failure, and prior stroke. Diabetes, hypertension, and blood pressure were not associated with permanent AF.

CONCLUSIONS: For people whose initial AF episode terminates, benefits of having lower BMI may include a lower risk of permanent AF. Risk of permanent AF was similar for people with and without diabetes or hypertension and across blood pressure levels.

KEY WORDS: cohort study; anthropometry; electrocardiogram; atrial fibrillation.

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INTRODUCTION

After atrial fibrillation (AF) is first detected and the initial episode terminates, AF commonly recurs and may become permanent.¹ For example, in the Canadian Registry of Atrial Fibrillation (CARAF) study, 63 % of people enrolled at their first diagnosed AF episode had a documented recurrence, and 25 % progressed to permanent AF within 5 years.² AF progression is associated with higher morbidity and mortality. In the Euro Heart Survey, people who progressed from having first-detected or paroxysmal AF to having persistent or permanent AF subsequently had higher rates of stroke, transient ischemic attack, myocardial infarction, hospital admission, and death than people whose AF had not progressed.³ Permanent AF may also be associated with more severe symptoms and lower quality of life.⁴

Understanding the risk factors for permanent AF could help identify people who would benefit most from interventions.⁵ Cardiovascular risk factors, including higher body mass index (BMI), diabetes, and elevated blood pressure are associated with new-onset AF.^{6–8} These factors are also of interest as potential risk factors for permanent

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AF. In a cohort study of people with newly diagnosed AF in Olmstead County, Minnesota, BMI, history of hypertension, and elevated blood pressure were positively associated with permanent AF, but diabetes was not.⁹ In the CARAF study, hypertension and diabetes were not associated with permanent AF, and BMI and blood pressure were not investigated.² To gain further understanding about cardiovascular risk factors and AF progression, we investigated age, sex, BMI, diabetes, hypertension, and systolic and diastolic blood pressure levels in relation to risk of permanent AF among people whose initial AF episode terminated.

METHODS

Study Design, Setting, and Participants

Participants were enrolled in this observational population-based inception cohort study at the date of onset of their initial AF episode at Group Health, an integrated health system in the state of Washington. The initial AF episode was defined as a person's first electrocardiography (ECG)-confirmed AF or atrial flutter followed by documented sinus rhythm within 6 months.

The study methods were detailed previously.¹⁰ The Group Health Human Subjects Review Committee approved the study. Group Health enrollees were eligible to be included if they were aged 30–84; their first ECG-confirmed AF or atrial flutter episode was between October 1, 2001, and December 31, 2004; they had no prior diagnosis code for AF or atrial flutter during their entire Group Health enrollment (mean of 22 years before the initial AF episode); and their initial AF episode terminated spontaneously or by cardioversion within 6 months after onset. Perioperative AF cases were eligible only if AF persisted to the time of hospital discharge. People with new-onset AF that occurred as part of a hospitalized terminal illness and people with a pacemaker implanted prior to their initial AF episode were not eligible. AF was identified by inpatient or outpatient ICD-9 codes for AF (427.31) or atrial flutter (427.32), and eligibility was confirmed by medical record review. We required that the medical records show that the initial AF or atrial flutter episode was confirmed by 12-lead ECG and was recognized by a physician. To be included, Group Health enrollees also had to have at least four Group Health visits before their initial AF episode, with the most recent visit being in the 6 years before the initial AF episode. For 69 % of participants, the qualifying minimum four visits were within 1 year before the initial AF episode. The reason for the four visits requirement was to exclude people who received very little care or no care at all at Group Health for many years, as they tend to have insufficient information in their Group Health medical records for measuring clinical variables of interest.

A prior publication detailed the number of potentially eligible cases of newly detected AF identified using ICD-9

codes and those who were excluded for various reasons, for the first full year of data collection, October 1, 2001–September 30, 2002.¹¹ During that year, there were 1,438 potentially eligible cases identified, of which 333 had AF that was not of new onset, 136 had perioperative AF that resolved by hospital discharge, 266 had fewer than four Group Health visits prior to their initial AF episode, 66 had a pacemaker implanted prior to their initial AF episode, and 41 had AF that occurred as part of a hospitalized terminal illness. We would expect the proportion of people excluded for various reasons to be about the same over the entire study period of the present analysis, October 1, 2001–December 31, 2004. For the entire study period, after the exclusions noted above, there were 1,953 people with newly diagnosed AF. For this analysis we excluded 391 whose initial AF episode did not terminate within 6 months after onset, 14 people with missing BMI values, and 31 with BMI < 18.5 kg/m² (underweight), leaving 1,517 people eligible for analyses of recurrent AF. For analyses of permanent AF, the main focus of this paper, we further excluded 132 people who had less than 6 months of follow-up after their initial AF episode terminated, leaving 1,385 people eligible for analyses of permanent AF.

Assessment of Risk Factors

Age, sex, and baseline clinical characteristics were determined from medical records using information recorded up to the day prior to the initial AF episode. Risk factors were not determined from diagnostic codes. BMI (weight[kg]/height[m]²) was calculated using the most recent weight measured prior to the initial AF episode (mean of 5.5 months prior) and height measured anytime during adulthood. BMI categories were defined as 18.5–24.9 kg/m² (normal weight), 25.0–29.9 kg/m² (overweight), 30.0–34.9 kg/m² (obese 1), 35.0–39.9 kg/m² (obese 2), and ≥40.0 kg/m² (obese 3). A prior Group Health study established the accuracy of clinical measures of weight and height.¹² Systolic and diastolic blood pressures were the most recent outpatient measurements prior to the initial AF episode (mean of 3.8 months prior). For diabetes and hypertension, we were interested in diagnoses the participant had as of the day prior to the initial AF episode. Diabetes was defined as a notation of a diabetes diagnosis in the medical record, plus current use of insulin or oral hypoglycemic medication. Hypertension was defined as a notation of a hypertension diagnosis in the medical record, plus current use of antihypertensive medication. For comparison to the Olmstead County study,⁹ we also created an alternative definition of hypertension as a notation of a hypertension diagnosis in the medical record or elevated blood pressure levels, with or without medication use.

We defined the following additional diagnoses for use as adjustment variables. All were defined from information noted in the medical record. Coronary heart disease was defined as history of hospitalization for myocardial infarction, coronary artery bypass, or angioplasty, or a physician diagnosis of probable or definite angina. Chronic heart failure was defined as a physician diagnosis plus ongoing medical treatment. Valvular heart disease was defined as a physician diagnosis of moderate to severe valvular heart disease or a prosthetic valve. History of stroke was defined as a physician diagnosis of definite or probable stroke.

Ascertainment of Recurrent AF and Permanent AF

To document rhythm status during follow-up, we combined information from three data sources: 1) medical records, 2) the Group Health ECG database, and 3) Group Health administrative databases. From medical records, we obtained dates and results of ECGs, Holter monitors, rhythm strips, electrical cardioversions, and other types of rhythm documentation from the initial AF episode through the date of medical record review. We also obtained dates and results of AF ablation and maze procedures, which would alter the subsequent risk of developing permanent AF. The medical record review took place a mean of 2 years after the initial AF episode, with a range of 6 months to 5 years. From the ECG database, we obtained dates and results of all ECGs done at Group Health facilities, all of which were interpreted by Group Health cardiologists for the presence or absence of AF, from the initial AF episode through December 31, 2009. From administrative databases, we obtained dates of ICD-9 and CPT procedure codes for electrical cardioversion, AF ablation, and maze procedures (ICD-9: 37.33, 37.34, 99.61, and 99.62; CPT: 92960 and 93651), from the initial AF episode through December 31, 2009, to augment information available from the medical records. Data from the ECG database and administrative databases were available for a mean of 7 years after the initial AF episode, with a range of 5 to 8 years.

Termination of the initial AF episode was determined by documented sinus rhythm after the first ECG-confirmed AF. Recurrent AF was defined as a documented AF episode after the initial AF episode. Permanent AF was defined as AF present on two separate occasions at least 6 months apart and no more than 36 months apart, without any documented sinus rhythm between the two occasions. Participants who met the definition of permanent AF were a subset of those who had recurrent AF. In sensitivity analyses, we modified the definition of permanent AF to require that AF was present on four separate occasions with the first and fourth occasions 6–36 months apart; or on two separate occasions 12–36 months apart; or on two separate occasions 6–18 months apart.

Follow-up for recurrent AF ended on the date of a documented AF recurrence, death, disenrollment from Group Health, or the end of the study on December 31, 2009, whichever occurred first. For permanent AF, a minimum of 6 months was required to establish the occurrence of the outcome, as described above. Therefore, people who had less than 6 months of follow-up after the initial AF episode terminated were excluded from the analysis, because their follow-up time was insufficient to establish the occurrence of permanent AF. For the same reason, people who had sufficient follow-up time but did not meet the definition of permanent AF were censored 6 months prior to the end of follow-up. Therefore, follow-up for permanent AF ended on the first date of the qualifying permanent AF interval, or 6 months prior to any of the following: death, an AF ablation or maze procedure, disenrollment from Group Health, or the end of the study on December 31, 2009, whichever occurred first. Example participant timelines showing recurrent and permanent AF outcomes are given in eFigure 1 (available online).

Statistical Analysis

Cumulative incidence was estimated by methods that allowed for death and AF ablation or maze procedures to be considered as competing risks.^{13,14} Cause-specific hazard ratios (HRs) and 95 % CIs were estimated using Cox proportional hazards models with study time as the time scale.¹⁵ Time zero was the date of onset of the initial AF episode. Follow-up time was left-truncated, with each person entering follow-up when the initial AF episode terminated, which may have been up to 6 months after the date of onset.

We examined the associations of age, sex, BMI categories, diabetes, hypertension, systolic blood pressure, and diastolic blood pressure with risk of permanent AF. In model 1, the hazard ratio for each risk factor was adjusted for age and sex. In model 2, the hazard ratio for each risk factor was adjusted for age, sex, and the other risk factors. In model 3, all hazard ratios were additionally adjusted for baseline coronary heart disease, valvular heart disease, heart failure, and prior stroke. We repeated all models using continuous BMI instead of BMI categories.

Analyses were conducted in Stata versions 10–12 (StataCorp, College Station, TX).

RESULTS

Baseline characteristics of the cohort of 1,385 people followed for permanent AF are shown in Table 1. Participants had a mean age of 69 years, 51 % were men, 75 % were overweight or obese, 16 % had diabetes, and 54 % had hypertension. Baseline characteristics of the cohort of 1,517

Table 1. Baseline Characteristics of Group Health Enrollees Followed for Permanent Atrial Fibrillation (AF)

Characteristic*	N=1,385
Demographic characteristics	
Age, y, mean (SD)	69.2 (11.1)
Male, N (%)	711 (51.3)
White race, N (%)	1,282 (92.8)
Group Health enrollment, y, mean (SD)	21.7 (13.5)
Location of initial AF diagnosis	
Outpatient, N (%)	458 (33.5)
Urgent care, N (%)	154 (11.3)
Emergency department, N (%)	557 (40.7)
Inpatient, N (%)	177 (12.9)
Other, N (%)	21 (1.5)
Most severe symptom present at initial AF diagnosis†	
Loss of consciousness, N (%)	32 (2.5)
Heart failure, N (%)	108 (8.3)
Chest pain, N (%)	285 (21.9)
Shortness of breath, N (%)	214 (16.5)
Mental status change, N (%)	17 (1.3)
Dizziness, N (%)	113 (8.7)
Palpitations, N (%)	275 (21.2)
Other, N (%)	70 (5.4)
No symptoms, N (%)	185 (14.2)
Clinical characteristics	
Body weight, kg, mean (SD)	88.0 (22.6)
Height, cm, mean (SD)	171.4 (10.3)
Body mass index, kg/m ² , mean (SD)	29.9 (7.1)
18.5–24.9 (normal), N (%)	341 (24.6)
25.0–29.9 (overweight), N (%)	497 (35.9)
30.0–34.9 (obese 1), N (%)	298 (21.5)
35.0–39.9 (obese 2), N (%)	128 (9.2)
≥ 40.0 (obese 3), N (%)	121 (8.7)
Diabetes, N (%)	216 (15.6)
Hypertension, N (%)	743 (53.7)
Systolic blood pressure, mm Hg, mean (SD)	136.2 (20.3)
Diastolic blood pressure, mm Hg, mean (SD)	76.6 (11.6)
Coronary heart disease, N (%)	277 (20.0)
Valvular heart disease, N (%)	75 (5.4)
Heart failure, N (%)	95 (6.9)
Prior stroke, N (%)	87 (6.3)

*Four participants had missing values for race, five for years of Group Health enrollment, 18 for location of initial AF diagnosis, and 86 for symptoms present at initial AF diagnosis

† Symptoms are listed in order of severity, with loss of consciousness as most severe

people followed for recurrent AF were similar, as shown in eTable 1 (available online). The initial AF episode terminated within 7 days in 71 % of participants. There were 272 deaths during follow-up for permanent AF and 168 deaths during follow-up for recurrent AF. Distributions of survival times are shown in eTable 2 (available online). Cumulative incidence of permanent AF was 8 % at 6 months, 10 % at 1 year, 15 % at 2 years, and 24 % at 5 years. Cumulative incidence of recurrent AF was 56 % at 6 months, 61 % at 1 year, 68 % at 2 years, and 74 % at 5 years.

The results of adjusted models for permanent AF are shown in Table 2. The hazard ratios were similar across all models. Older age and higher BMI were associated with higher risk of permanent AF. The HR of permanent AF per 5-kg/m² increment of continuous BMI was 1.10 (95 % CI: 1.01, 1.20), adjusted for age, sex, diabetes, hypertension, blood pressure levels, coronary heart disease, valvular heart disease, heart failure, and prior stroke.

Sex, diabetes, hypertension, and blood pressure levels were not associated with the risk of permanent AF in any model. In a sensitivity analysis with hypertension defined similarly to the Olmstead County study, we found no association with permanent AF (data not shown). In sensitivity analyses with modifications to the permanent AF definition, we observed lower numbers of permanent AF events, as expected, but the HRs and 95 % CIs were similar to those seen in the primary analysis (eTable 3, available online). In analyses of recurrent AF, shown in eTable 4 (available online), older age, male sex, and higher BMI were associated with higher risk of recurrent AF, but diabetes, hypertension, and blood pressure levels were not.

DISCUSSION

In this population-based inception cohort study of people whose initial AF episode terminated, we observed that older age and higher BMI were associated with a higher risk of developing permanent AF. Other cardiovascular risk factors including sex, diabetes, hypertension, and blood pressure levels showed little or no evidence of an association with permanent AF.

Our findings for BMI as a risk factor for permanent AF are consistent with observations made in a population-based cohort of over 3,000 people newly diagnosed with AF in Olmstead County, Minnesota.⁹ In the Olmstead County study, permanent AF was defined as AF that could not be converted to normal sinus rhythm, and was ascertained from medical records and an ECG database. Hazard ratios for permanent AF were 1.13 (95 % CI: 0.92, 1.39) for overweight vs. normal weight, 1.54 (1.21, 1.95) for obesity vs. normal weight, and 1.87 (1.40, 2.51) for severe obesity vs. normal weight, adjusted for age and sex, similar to our results. Several additional studies provide further supporting evidence of a role for BMI in AF progression. A prior study by our group showed that AF among Group Health enrollees was more likely to be permanent at its initial detection in people with higher BMI.⁶ A cross-sectional analysis of prevalent AF from the China Multi-center Collaborative Study of Cardiovascular Epidemiology (MUCA) found that BMI was more strongly associated with persistent or permanent AF than with first-detected or paroxysmal AF.¹⁶ In a secondary analysis of data from a subset of participants in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AF-FIRM) trial, which included people with newly diagnosed or recently recurrent AF who had at least one other risk factor for stroke or death, higher BMI was associated with higher number of attempted cardioversions during follow-up and higher number of follow-up visits in AF.¹⁷ Some smaller studies have suggested that higher BMI may be

Table 2. Hazard Ratios of Permanent Atrial Fibrillation (AF)*

Risk factor	Events	Person-years	Model 1†	Model 2‡	Model 3§
			HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
Overall	317	5,253	—	—	—
Age, per 10 y	—	—	1.20 (1.08, 1.33)	1.27 (1.12, 1.43)	1.27 (1.13, 1.44)
Female	160	2,560	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	157	2,693	1.01 (0.80, 1.26)	1.03 (0.82, 1.29)	1.04 (0.83, 1.32)
Body mass index (kg/m ²)					
18.5–24.9 (normal)	65	1,232	1.00 (reference)	1.00 (reference)	1.00 (reference)
25.0–29.9 (overweight)	114	1,898	1.23 (0.91, 1.68)	1.24 (0.91, 1.69)	1.26 (0.92, 1.72)
30.0–34.9 (obese 1)	74	1,173	1.32 (0.94, 1.85)	1.33 (0.94, 1.87)	1.35 (0.96, 1.91)
35.0–39.9 (obese 2)	33	515	1.47 (0.96, 2.25)	1.48 (0.96, 2.29)	1.50 (0.97, 2.33)
≥ 40.0 (obese 3)	31	435	1.78 (1.14, 2.79)	1.79 (1.13, 2.84)	1.79 (1.13, 2.84)
Diabetes:					
No	272	4,472	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	45	781	0.99 (0.72, 1.36)	0.93 (0.67, 1.29)	0.94 (0.67, 1.32)
Hypertension:					
No	142	2,564	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	175	2,689	1.04 (0.83, 1.31)	0.98 (0.78, 1.25)	0.99 (0.78, 1.26)
Systolic blood pressure, per 10 mmHg	—	—	1.01 (0.96, 1.07)	0.99 (0.93, 1.06)	0.99 (0.93, 1.06)
Diastolic blood pressure, per 10 mmHg	—	—	1.05 (0.96, 1.16)	1.04 (0.93, 1.18)	1.05 (0.93, 1.19)

*Permanent AF was defined as AF present on two separate occasions 6–36 months apart, without any documented sinus rhythm

† Model 1: Adjusted for age and sex

‡ Model 2: Adjusted for age, sex, and all risk factors shown in the table

§ Model 3: Adjusted for age, sex, all risk factors shown in the table, and baseline coronary heart disease, valvular heart disease, heart failure, and prior stroke

|| The HRs per 5-kg/m² increment of continuous BMI were 1.10 (95 % CI: 1.01, 1.20) in model 1; 1.10 (95 % CI: 1.01, 1.20) in model 2; and 1.10 (95 % CI: 1.01, 1.20) in model 3

associated with higher electrical energy levels required to achieve cardioversion,¹⁸ higher AF recurrence during the first year after successful cardioversion,¹⁹ and higher AF recurrence during the first 1 to 2 years after catheter ablation of AF.^{20–22}

We did not investigate specific mechanisms whereby higher BMI could have increased the risk of permanent AF. Several potential mechanisms have been suggested in previous publications, including obesity-related increases in left atrial size, P-wave dispersion, left ventricular diastolic filling pressure, lipid deposits in myocardial tissue, inflammation, oxidative stress, sleep apnea, and autonomic dysfunction.^{6,9,23,24}

Although overweight and obesity are cardiovascular risk factors, they are associated with lower mortality compared with normal weight among people with certain cardiovascular diseases, including AF.^{25,26} The reasons for this obesity paradox are unknown, although several speculative explanations have been proposed in previous publications.^{25,26} Research on weight change interventions in people with AF could consider not only the effects on AF progression, but also on mortality.

We hypothesized that diabetes, hypertension, and blood pressure levels would be associated with higher risk of permanent AF, because these factors were associated with higher risk of new-onset AF in prior studies.^{7,8} However, we did not find evidence for associations of these factors with permanent AF. These results are consistent with the CARAF study, which found no associations of permanent AF with diabetes or hypertension.² In the Olmstead County study, the risk of

progression to permanent AF was similar for diabetics and nondiabetics. However, progression to permanent AF was associated with history of hypertension, systolic blood pressure, and diastolic blood pressure, adjusted for age and sex.⁹ A potential explanation for the different results for hypertension in the Olmstead County study and our study is different definitions of hypertension. The Olmstead County study defined history of hypertension anytime before baseline as physician diagnosis, treatment with antihypertensive medication, or elevated blood pressure. In contrast, we defined hypertension at baseline as physician diagnosis plus current treatment with antihypertensive medication. However, when we redefined hypertension to be similar to the Olmstead County study definition, we still did not find an association with higher risk of permanent AF in this study. Other explanations could include differences in the degree of blood pressure control or differences in antihypertensive medication use.

Our study had several strengths. We ascertained a large cohort of people newly diagnosed with AF from a well-defined population, representative of routine clinical practice, rather than a referral population or self-selected study participants. We used broad inclusion criteria to enhance the generalizability of the findings to other populations. We used multiple data sources to obtain heart rhythm documentation throughout follow-up, and cardiologists interpreted all ECGs.

A limitation of this study was the possibility of incomplete detection of recurrent AF and permanent AF. Nonetheless, our estimates for cumulative incidence of

recurrent and permanent AF were similar to previous estimates from the CARAF study.² In this study, we relied on rhythm documentation obtained during usual clinical care in Group Health, rather than on frequent study ECGs. We may have missed ECGs from non-Group Health hospitals or other facilities, unless they were sent to Group Health and were incorporated into Group Health medical records. Because of incomplete rhythm documentation, some people in this study may have experienced recurrent or permanent AF without our knowing, and some people who never actually experienced permanent AF during follow-up may have met our definition of permanent AF as false positives. There may also have been measurement error in the timing of outcomes due to the incomplete data. To address errors in detecting permanent AF, we evaluated several different definitions of permanent AF that were aimed at reducing false positives. The different definitions had little effect on the results. Another limitation was that we only included people with AF that came to medical attention; we did not ascertain people with subclinical or preclinical AF. The participants included in our study may have had different characteristics than those who were not ascertained. Another limitation was possible measurement error in assessing the cardiovascular risk factors. We relied on medical records that may be incomplete or have errors. A prior study has demonstrated high validity of BMI obtained from Group Health medical records.¹² In that study, a comparison of measures obtained by researchers with measures recorded in medical records showed a correlation of 0.99 for weight with a mean difference of 0.1 kg, and the correlation of 0.94 for height with a mean difference of <0.1 in.

In summary, for people whose initial AF episode terminated, the benefits of having lower BMI may include a lower risk of permanent AF. Further work is needed to increase our knowledge about risk factors for permanent AF, including efforts to identify modifiable risk factors and to test interventions among people with modifiable risk factors, so that we can more effectively address the burden of AF in the aging population.

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