Diabetes Mellitus, Glycemic Control, and Risk of Atrial Fibrillation

Sascha Dublin, MD, PhD^{1,2}, Nicole L. Glazer, PhD³, Nicholas L. Smith, PhD^{2,6}, Bruce M. Psaty, MD, PhD^{1,2,3,4}, Thomas Lumley, PhD⁵, Kerri L. Wiggins, MS, RD³, Richard L. Page, MD⁷, and Susan R. Heckbert, MD, PhD^{1,2}

¹Group Health Research Institute, Seattle, WA, USA; ²Department of Epidemiology, University of Washington, Seattle, WA, USA; ³Department of Medicine, University of Washington, Seattle, WA, USA; ⁴Department of Health Services, University of Washington, Seattle, WA, USA; ⁵Department of Biostatistics, University of Washington, Seattle, WA, USA; ⁶Seattle Epidemiology Research and Information Center, VA Puget Sound Health Care System, Seattle, WA, USA; ⁷Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA.

BACKGROUND: Diabetes may be an independent risk factor for atrial fibrillation. However, results from prior studies are in conflict, and no study has examined diabetes duration or glycemic control.

OBJECTIVE: To examine the association of diabetes with risk of atrial fibrillation and to describe risk according to diabetes duration and glycemic control.

DESIGN: A population-based case-control study.

PARTICIPANTS: Within a large, integrated healthcare delivery system, we identified 1,410 people with newly-recognized atrial fibrillation from ICD-9 codes and validated cases by review of medical records. 2,203 controls without atrial fibrillation were selected from enrollment lists, stratified on age, sex, hypertension, and calendar year.

MAIN MEASURES: Information on atrial fibrillation, diabetes and other characteristics came from medical records. Diabetes was defined based on physician diagnoses recorded in the medical record, and pharmacologically treated diabetes was defined as receiving antihyperglycemic medications. Information about hemoglobin A1c levels came from computerized laboratory data.

KEY RESULTS: Among people with atrial fibrillation, 252/1410 (17.9%) had pharmacologically treated diabetes compared to 311/2203 (14.1%) of controls. The adjusted OR for atrial fibrillation was 1.40 (95% CI 1.15-1.71) for people with treated diabetes compared to those without diabetes. Among those with treated diabetes, the risk of developing atrial fibrillation was 3% higher for each additional year of diabetes duration (95% CI 1-6%). Compared to people without diabetes, the adjusted OR for people with treated diabetes with average hemoglobin A1c ≤ 7 was 1.06 (95% CI 0.74-1.51); for A1c > 7 but ≤ 8 , 1.48 (1.09-2.01); for A1c > 8 but ≤ 9 , 1.46 (1.02-2.08); and for A1c > 9 , 1.96 (1.22-3.14).

CONCLUSIONS: Diabetes was associated with higher risk of developing atrial fibrillation, and risk was higher with longer duration of treated diabetes and worse glycemic control. Future research should identify and test approaches to reduce the risk of atrial fibrillation in people with diabetes.

KEY WORDS: arrhythmia; atrial fibrillation; diabetes mellitus; glycemic control; diabetes complications.

J Gen Intern Med 25(8):853-8

DOI: 10.1007/s11606-010-1340-y

© U.S. Government 2010

INTRODUCTION

In the United States 25.4 million people are projected to have diabetes by 2011, rising to 37.7 million by 2031.¹ Physiologic changes associated with diabetes include increased left atrial size² and elevated C-reactive protein,³⁻⁶ a marker of chronic inflammation. Both findings are associated with heightened risk of atrial fibrillation,^{3,7-9} a common and serious arrhythmia that confers significant risks for stroke and death.^{10,11} Many epidemiologic studies have examined atrial fibrillation risk in relation to diabetes or elevated blood glucose, with conflicting results: ten studies observed an association,^{3,9,12-19} while nine did not.^{11,20-27} Often, prior studies examined many possible predictive factors and were not designed to evaluate the role of diabetes specifically.^{3,9,11,14,17,19,22-27} Many studies did not adjust for obesity, which is associated with increased risk of both diabetes and atrial fibrillation.^{20,28,29} No study has examined the potential role of diabetes duration or glycemic control. We used data from a large case-control study of newly-recognized atrial fibrillation³⁰ to examine the relationship between diabetes and risk of atrial fibrillation and to explore whether risk differs by diabetes duration and glycemic control. Our hypotheses were that diabetes would be associated with higher risk of atrial fibrillation and that risk would be higher for people with longer duration of diabetes or worse glycemic control.

RESEARCH DESIGN AND METHODS

Setting

This study took place at Group Health (GH), a large, integrated health care delivery system in the United States. Study

Received November 10, 2009

Revised February 15, 2010

Accepted March 17, 2010

Published online April 20, 2010

procedures were approved by the GH Human Subjects Review Committee.

Population; Identification of Cases and Controls

We carried out a population-based case-control study of newly-recognized atrial fibrillation. This study is one of four case-control studies of cardiovascular outcomes with a shared control group.³⁰⁻³³ Because prior studies examined hormone replacement therapy and antihypertensive medications, the study population consists of women who were post- and perimenopausal and men with pharmacologically treated hypertension. These analyses include people age 30-84 with at least four GH visits (to ensure adequate data in the medical record). Women were defined as post-menopausal if their periods had stopped due to natural or surgical menopause. Treated hypertension was defined as having received a diagnosis of hypertension or high blood pressure and also receiving pharmacologic treatment. People were excluded if they had a pacemaker (which could interfere with identification of atrial fibrillation) or were missing data for body mass index (BMI; $n=72$). These inclusion and exclusion criteria were ascertained by medical record review.

We used GH electronic data to identify all cases of atrial fibrillation occurring between October 1, 2001, and December 31, 2004 based on International Classification of Diseases, 9th revision (ICD-9) codes for atrial fibrillation or flutter from inpatient and outpatient encounters. Medical records were reviewed to validate the presence of atrial fibrillation and ensure that it was newly recognized. Perioperative atrial fibrillation was included only if it persisted until hospital discharge (10 cases).

A shared group of control subjects was selected from GH enrollment lists, frequency matched to the myocardial infarction cases (the largest case group in the four linked studies) by age, sex, calendar year, and hypertension status. For these analyses, we included only controls who had no history of atrial fibrillation that met study criteria.

Data Collection and Variable Creation

All subjects were assigned an index date, and data on covariates were collected only prior to the index date. For cases, the index date was the date of atrial fibrillation diagnosis, while controls were assigned a random date within that calendar year. Medical record review provided information on clinical characteristics including diabetes, hypertension, hypercholesterolemia, height, weight, valvular heart disease, congestive heart failure, myocardial infarction, angina, history of revascularization, and blood pressure. Telephone interview, completed by 51% of cases and 61% of controls, provided information about smoking, race, and alcohol intake. For people who did not complete the telephone interview, these data were obtained from medical records. Laboratory results and pharmacy data came from GH's automated databases. Among GH members in this age range, 96% report filling all or almost all prescriptions through GH pharmacies.³⁴

We categorized atrial fibrillation based on its persistence and duration using clinical data from the medical record. Our

classification scheme was based on that of the American College of Cardiology/American Heart Association/European Society of Cardiology,³⁵ with minor modifications required because of the data available to us. *Transitory* atrial fibrillation was defined as an episode lasting 7 days or less with no evidence of recurrence in the next 6 months, *persistent/intermittent* as lasting longer than 7 days or recurring but with sinus rhythm also present during the next 6 months, and *sustained* as lasting for at least 6 months with no evidence of sinus rhythm (similar to the ACC/AHA/ESC category of *permanent*).

We defined diabetes as present if there was a physician diagnosis in the medical record. Diabetes was classified as pharmacologically treated if the record indicated use of anti-hyperglycemic medications at the index date and as untreated if the person was not receiving medications. A similar approach was used to categorize hypertension and hypercholesterolemia. Diabetes duration was defined as time from the date of the first antihyperglycemic medication prescription to the index date. No other information on diabetes duration was available to us. Clinical coronary artery disease was defined as history of coronary artery bypass grafting, angioplasty, definite or probable angina, or hospitalized myocardial infarction. We calculated BMI as the most recent weight (kilograms) divided by the square of height (meters) and defined obesity as BMI ≥ 30 kg/m².³⁶

The GH computerized laboratory database, in existence since 1988, provided data on glycemic control. Prior to 1996, the GH laboratory measured total glycosylated hemoglobin, which we converted to equivalent hemoglobin A1c values using the formula $1.7 + 0.6 * (\text{total glycosylated hemoglobin})$ (equation developed by William C. Butts, PhD, and provided by Dr. Kim Riddell, GH laboratories). To examine long-term glycemic control, we calculated a simple linear time-weighted average of all values prior to index date.

Statistical Analysis

We performed descriptive analyses comparing characteristics of atrial fibrillation cases and controls. We also examined characteristics associated with diabetes among control subjects. Multivariable logistic regression was used to estimate the risk of newly-recognized atrial fibrillation associated with diabetes. All ORs and 95% CIs were calculated with adjustment for the matching variables of age, sex, calendar year, and treated hypertension. We selected additional covariates for final models using the change-in-estimate approach, including only those which altered the primary risk estimate by 10% or more. Variables considered were race, BMI, smoking, alcohol intake, number of visits in the prior year, valvular heart disease, claudication, chronic lung disease, hypercholesterolemia, blood pressure, total and HDL cholesterol, and use of specific antihypertensive agents. We did not include coronary artery disease and congestive heart failure because they may be in the causal pathway between diabetes and atrial fibrillation. Only BMI altered the main risk estimate by 10% or more, so final models were adjusted only for matching variables and BMI. We carried out sensitivity analyses adjusting for a large number of cardiovascular risk factors and diseases to explore the potential for residual confounding.

Because there were few people with untreated diabetes and our primary analyses indicated no association between untreated diabetes and atrial fibrillation, we excluded people with untreated diabetes from further analyses. We repeated our main analysis for subgroups defined by age, sex, and the presence of hypertension, obesity, hypercholesterolemia, coronary artery disease, or congestive heart failure. We used multiplicative interaction terms and the likelihood ratio test to determine whether the relationship between treated diabetes and atrial fibrillation differed significantly between subgroups. We also examined whether the association differed according to the duration and persistence of atrial fibrillation, using polytomous logistic regression to compare the three types of cases (transitory, persistent/intermittent, and sustained) to controls and assessing statistical significance with the Wald test.

Multivariable logistic regression was used to examine the association of two aspects of the exposure, duration of diabetes and glycemic control, with atrial fibrillation risk. We did this to investigate whether there was a dose-response relationship, hypothesizing that people with longer or more intense exposure to diabetes would have a higher risk of atrial fibrillation. The referent group was people without diabetes. Finally, in analyses limited to people with treated diabetes, we modeled duration and glycemic control simultaneously as continuous variables, adjusting each variable for the other.

Analyses were carried out using Stata/MP versions 9.2 and 10.1 for Windows (StataCorp LP, College Station, TX).

RESULTS

We identified 1,410 cases of newly-recognized atrial fibrillation during the study period. Five hundred and forty eight (39%) had transitory atrial fibrillation, 631 (45%) persistent/intermittent, 207 (15%) sustained, and 24 (1.7%) could not be categorized due to missing data. 2203 controls were selected from GH enrollment lists, stratified by age, sex, calendar year, and hypertension status.

Cases were slightly older than controls and more likely to have valvular heart disease, coronary artery disease, or chronic congestive heart failure (Table 1). Among controls, people with treated diabetes were younger and more often male compared to those without diabetes (Table 2). Controls with treated diabetes were also more likely to be obese and to have hypercholesterolemia, coronary artery disease, and congestive heart failure.

Treated diabetes was present in 17.9% of cases and 14.1% of controls (OR 1.40, 95% CI 1.15-1.71, adjusted for age, sex, calendar year, treated hypertension, and BMI; Table 3). In sensitivity analyses, the OR was 1.45 (95% CI 1.16-1.81) after additional adjustment for race, smoking, hypercholesterolemia, prior visits, systolic blood pressure, use of ACE inhibitors or beta-blockers, and total and HDL cholesterol. Untreated diabetes was not associated with risk of atrial fibrillation (adjusted OR 1.04, 95% CI 0.75-1.45). The association between treated diabetes and atrial fibrillation was stronger in people who were obese (OR 1.64, 95% CI 1.27-2.12) than in those who were not (OR 1.10, 95% CI 0.80-1.52; $p=0.02$ for the interaction) but did not differ substantially by sex, age, or the presence of treated hypertension, hypercholesterolemia, coronary artery disease, or congestive heart failure (all p values >0.10). The OR for transitory atrial fibrillation in relation to treated diabetes was 1.35 (95% CI

Table 1. Characteristics of People with Atrial Fibrillation (Cases) and Controls

Characteristic	Atrial fibrillation cases	Controls
	N=1410	N=2203
	n ^a (%)	n ^a (%)
Median age, years (IQR) ^b	74 (66, 80)	68 (59, 76)
Female ^b	911 (64.6)	1208 (54.8)
Treated hypertension ^b	1043 (74.0)	1710 (77.6)
White race	1306/1399 (93.4)	1918/2166 (88.6)
Median body mass index, kg/m ² (IQR)	29 (25, 34)	29 (25, 33)
Obese (BMI ≥ 30 kg/m ²)	595 (42.2)	938 (42.6)
Hypercholesterolemia	428 (30.7)	611 (27.7)
Valvular heart disease	89 (6.3)	45 (2.0)
Coronary artery disease ^c	322 (22.8)	358 (16.3)
Chronic congestive heart failure	128 (9.1)	64 (2.9)
Current smoker	118/1409 (8.4)	220/2201 (10.0)
Median systolic blood pressure, mm Hg (IQR)	137 (122, 150)	136 (122, 148)
Median diastolic blood pressure, mm Hg (IQR)	78 (70, 84)	80 (70, 84)
Median cholesterol, mg/dL (IQR)	5.78 (5.10, 6.55)	5.72 (5.00, 6.55)
Median HDL cholesterol, mg/dL (IQR)	1.37 (1.11, 1.74)	1.35 (1.09, 1.66)
Median length of GH enrollment, years (IQR)	21 (11, 31)	20 (11, 30)
Median number of visits in prior year (IQR)	6 (3, 11)	4 (2, 8)

Abbreviations: BMI, body mass index; GH, Group Health; HDL, high-density lipoprotein; IQR, interquartile range; mm Hg, millimeters mercury
^a <5% in each group shown had missing data for each characteristic except for HDL cholesterol (missing for 5.5% of cases and 3.0% of controls)

^bStratification variable used in selection of controls

^cDefined as history of hospitalized myocardial infarction, coronary artery bypass grafting, angioplasty, or definite or probable angina.

1.03-1.78); for persistent/intermittent atrial fibrillation, 1.36 (1.06-1.76); and for sustained atrial fibrillation, 1.71 (1.17-2.49; $p=0.51$ for differences among the three case groups).

Duration of pharmacologic treatment for diabetes, which we examined as a surrogate for diabetes duration, was available for 91% of people with treated diabetes. The median duration was 8.2 years and was higher for cases than controls (9.6 versus 7.1 years). Figure 1 shows the risk of atrial fibrillation in relation to duration. Compared to people without diabetes, the adjusted OR for duration ≤ 5 years was 1.07 (95% CI 0.75-1.51); for >5 but ≤ 10 years, 1.51 (95% CI 1.05-2.16); and for >10 years, 1.64 (95% CI 1.22-2.20). Among people with treated diabetes, the adjusted OR per additional 1 year of duration was 1.03 (95% CI 1.01-1.06).

At least one measure of hemoglobin A1c was available for 99% of people with treated diabetes, and the median number of measures was 16 (IQR 10-25) over a median of 9.4 years. Compared to people without diabetes, increased atrial fibrillation risk was seen for average hemoglobin A1c above 7 (Fig. 2). Adjusted ORs, compared to people without diabetes, were 1.06 (95% CI 0.74-1.51) for average hemoglobin A1c ≤ 7 ; 1.48 (95% CI 1.09-2.01) for A1c above 7 but ≤ 8 ; 1.46 (95% CI 1.02-2.08) for A1c above 8 but ≤ 9 ; and 1.96 (95% CI 1.22-3.14) for A1c >9 . Among people with treated diabetes, the adjusted OR per 1 unit increase in hemoglobin A1c was 1.14 (95% CI 0.96-1.35).

Table 2. Characteristics Associated with Diabetes Among Control Subjects

Characteristic	No diabetes	Untreated diabetes	Treated diabetes ^a
	N=1792	N=100	N=311
	n ^b (%)	n ^b (%)	n ^b (%)
Median age, years (IQR)	68 (58, 76)	68 (60, 76)	67 (60, 76)
Female	1033 (57.7)	48 (48.0)	127 (40.8)
Treated hypertension	1334 (74.4)	89 (89.0)	287 (92.3)
White race	1579/1764 (89.5)	84/98 (85.7)	255/304 (83.9)
Median body mass index, kg/m ² (IQR)	28 (25, 32)	31 (27, 35)	32 (28, 37)
Obese (BMI ≥30 kg/m ²)	688 (38.4)	56 (56.0)	194 (62.4)
Hypercholesterolemia	397 (22.2)	44 (44.0)	170 (54.7)
Valvular heart disease	39 (2.2)	0 (0)	6 (1.9)
Coronary artery disease ^c	242 (13.5)	24 (24.0)	92 (29.6)
Chronic congestive heart failure	32 (1.8)	3 (3.0)	29 (9.3)
Current smoker	181/1790 (10.1)	13 (13.0)	26 (8.4)
Median systolic blood pressure, mm Hg (IQR)	136 (122, 146)	137 (128, 150)	138 (124, 150)
Median diastolic blood pressure, mm Hg (IQR)	80 (70, 84)	76 (70, 84)	76 (68, 82)
Median total cholesterol, mg/dL (IQR)	5.70 (4.97, 6.53)	6.06 (5.23, 6.68)	5.91 (5.05, 6.73)
Median HDL cholesterol, mg/dL (IQR)	1.40 (1.14, 1.74)	1.22 (1.06, 1.55)	1.14 (0.98, 1.35)
Median length of GH enrollment, years (IQR)	20 (11, 30)	21 (12, 30)	20 (11, 29)
Median number of visits in prior year (IQR)	4 (2, 8)	5 (3, 10)	6 (3, 10)

Abbreviations: BMI, body mass index; GH, Group Health; HDL, high-density lipoprotein; IQR, interquartile range; mm Hg, millimeters mercury

^aDefined as receiving antihyperglycemic medications

^b<5% in each group had missing data for each characteristic

^cDefined as history of hospitalized myocardial infarction, coronary artery bypass grafting, angioplasty, or definite or probable angina

CONCLUSIONS

In this population-based case-control study, people receiving pharmacologic treatment for diabetes had 40% higher risk of developing atrial fibrillation than people without diabetes. Risk was higher with longer duration of treated diabetes, and there was a suggestion of higher risk with worse glycemic control.

Prior studies examining risk of atrial fibrillation in relation to diabetes or impaired glucose metabolism have yielded conflicting results.^{3,9,11–27} Our results are similar to those reported by several prospective studies,^{12,14,18} including the Framingham Heart Study,¹⁴ all of which reported ORs in the range of 1.4 to 1.6. Other studies found an association between higher blood glucose and increased risk of atrial fibrillation.^{9,17}

Figure 1. Risk of newly-recognized atrial fibrillation by duration of treated diabetes. The diamond represents the adjusted OR and the vertical line, the 95% CI. ORs are adjusted for age, sex, calendar year, treated hypertension, and body mass index. People with no history of diabetes are the referent group.

However, numerous studies did not observe an association between diabetes and atrial fibrillation,^{11,20–27} and one study observed an association in women but not men (adjusted OR 1.26 [1.08–1.46] for women and 1.09 [0.96–1.24] for men).¹³ The discrepant findings may reflect methodologic differences including sample size, leading to low power in some studies, as well as the definition and method of ascertaining diabetes and atrial fibrillation. Unlike many prior studies, our primary focus was on the diabetes-atrial fibrillation relationship, and so we designed our statistical analyses accordingly. Unlike most prior studies, we adjusted for BMI, and so our findings support an independent association of diabetes with atrial fibrillation beyond the known association with obesity.^{20,28,29}

A large proportion (39%) of our cases had “transitory” atrial fibrillation, defined as a single episode lasting 7 days or less without recurring in the ensuing 6 months. Many prior studies did not report information about duration or persistence of

Table 3. Risk of Newly Recognized Atrial Fibrillation in Relation to Diabetes

	Controls	Cases	OR (95% CI) ^a
	N=2203	N=1410	
	n (%)	n (%)	
No diabetes	1792 (81.3)	1090 (77.3)	1.0 (Ref.)
Untreated diabetes	100 (4.5)	68 (4.8)	1.04 (0.75–1.45)
Pharmacologically treated diabetes ^b	311 (14.1)	252 (17.9)	1.40 (1.15–1.71)

^aAdjusted for age, sex, calendar year, treated hypertension and body mass index (continuous). Further adjustment for additional characteristics did not alter risk estimates

^bDefined as receiving antihyperglycemic medications

Figure 2. Risk of newly-recognized atrial fibrillation by average level of hemoglobin A1c. The diamond represents the adjusted OR and the vertical line, the 95% CI. ORs are adjusted for age, sex, calendar year, treated hypertension, and body mass index. People with no history of diabetes are the referent group.

atrial fibrillation^{11,13,14,16,17,19,20,25-27} or used a classification scheme not directly comparable to ours.^{9,12,22} Based on their methods, some prior studies would have been more likely to detect permanent than paroxysmal atrial fibrillation.^{12,19,25,27} If diabetes conveys increased risk of paroxysmal atrial fibrillation and these cases were classified as not having atrial fibrillation in other studies, then our risk estimates may be higher than those from studies with such misclassification. We found that people with diabetes were at increased risk for all subtypes of atrial fibrillation, regardless of its duration or persistence.

Our study is the first to examine risk of atrial fibrillation in relation to diabetes duration and glycemic control. We observed higher risk with longer duration of pharmacologic treatment for diabetes (used as a surrogate for diabetes duration) and worse glycemic control. This pattern supports a dose-response effect, with greater exposure to hyperglycemia conferring increased risk. A dose-response effect is considered to support causality. Our risk estimates suggest higher atrial fibrillation risk for people with treated diabetes for more than 5 years or average hemoglobin A1c above 7.0. These findings could indicate a threshold effect, which is further supported by our finding that risk was not elevated among people with diabetes who were not receiving pharmacologic treatment (OR 1.04, 95% CI 0.75-1.45). Within GH, people with diabetes who are not receiving pharmacologic treatment probably are earlier in the course of diabetes or have milder disease than those receiving treatment. GH laboratory data confirm that the average hemoglobin A1c in the untreated group was lower than in the treated group. Still, our risk estimates have wide confidence limits, and we cannot rule out a clinically meaningful elevated risk for atrial fibrillation in people with diabetes who are not receiving pharmacologic treatment or have short duration of diabetes or excellent glycemic control.

In subgroup analyses, we observed an association between diabetes and risk of atrial fibrillation for people who were obese but no association in those who were not obese. This result should be interpreted cautiously because it was unexpected and arose from analyses examining many subgroups. It is possible that the physiology of diabetes differs by body mass index, with obese individuals having higher levels of insulin resistance and perhaps altered levels of some hormones compared to non-obese individuals. Further investigation of this potential interaction is warranted because it could shed light on the mechanism by which diabetes may lead to atrial fibrillation.

Several physiologic mechanisms could underlie a causal relationship between diabetes and atrial fibrillation.³⁷ People with diabetes have higher levels of C-reactive protein,³⁻⁶ a marker of systemic inflammation, which may promote myocardial fibrosis and diastolic dysfunction. Diabetes is associated with left atrial enlargement² which is thought to allow the development and propagation of reentrant electrical circuits. Diabetes also causes neural remodeling in the atria, including parasympathetic denervation and heterogeneous sympathetic denervation.³⁸ People with diabetes are at higher risk of coronary artery disease and congestive heart failure, which may contribute to the development of atrial fibrillation. Finally, after accounting for obesity, people with diabetes have higher prevalence of obstructive sleep apnea,³⁹ which may lead to atrial fibrillation.⁴⁰

Our study has limitations. Our population consists of post- and perimenopausal women and hypertensive men and is predominantly white, which may limit generalizability. Because diabetes was identified in the course of routine clinical care, some people in the study probably had unrecognized diabetes. We identified only atrial fibrillation that came to clinical attention, so some transitory or asymptomatic cases may have been missed. It is possible that people with diabetes were more likely to have their atrial fibrillation recognized than people without diabetes, which could have resulted in bias. We lacked information about actual duration of diabetes and so we examined as a surrogate measure the duration of pharmacologic treatment for diabetes. Many people have diabetes for years before it is clinically detected. These factors may have led to misclassification of diabetes duration. We lacked information about some characteristics (e.g. physical activity and thyroid disease) and so there may be residual confounding.

In conclusion, we observed that pharmacologically treated diabetes was associated with a 40% increased risk of developing atrial fibrillation, and that risk was higher in people with longer duration of diabetes and worse glycemic control, providing support for a causal association. These results may increase understanding of the spectrum of cardiovascular disease associated with diabetes. Our findings suggest clinicians should have heightened suspicion for atrial fibrillation in people with diabetes, particularly those presenting with relevant symptoms. It may also be useful to screen for diabetes in people newly diagnosed with atrial fibrillation. In addition, given the high and rising prevalence of diabetes, our results have important implications for the future health burden of atrial fibrillation. Future research should investigate treatment approaches to reduce the risk of atrial fibrillation among people with diabetes.

Funding: This research was funded by grants HL 68986, HL 43201, HL 73410, and HL 68639 from the National Heart, Lung and Blood Institute. Dr. Dublin was funded through a Veterans' Affairs Health Services Research & Development fellowship, a Paul Beeson Career Development Award from the National Institute on Aging (K23AG028954), and Group Health Research Institute internal funds. The Beeson Award is also supported in part by the American Federation for Aging Research, the Hartford Foundation, the Atlantic Philanthropies and the Starr Foundation.

Prior presentations: This work was presented at the American Heart Association 47th Annual Conference on Cardiovascular Disease Epidemiology and Prevention in Orlando, Florida, on February 28, 2007 (poster), and the 13th Annual HMO Research Network Conference in Portland, Oregon, on March 21, 2007 (oral presentation).

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Conflict of interest statement: Dr. Dublin has received a Merck/American Geriatrics Society New Investigator Award. Dr. Page has consulted for Sanofi-Aventis and Astellas. Dr. Psaty has served as an unpaid consultant for AVIIR, a proteomics company, about its plans for an ancillary study within the MultiEthnic Study of Atherosclerosis. Other authors have no potential conflicts to disclose.

Corresponding Author: Sascha Dublin, MD, PhD: Group Health Research Institute, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101-1448, USA (e-mail: dublin.s@ghc.org).

REFERENCES

1. Mainous AG 3rd, Baker R, Koopman RJ, et al. Impact of the population at risk of diabetes on projections of diabetes burden in the United States: an epidemic on the way. *Diabetologia*. 2007;50:934-40.
2. Rutter MK, Parise H, Benjamin EJ, et al. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation*. 2003;107:448-54.
3. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation*. 2003;108:3006-10.
4. Bluher M, Fasshauer M, Tonjes A, Kratzsch J, Schon MR, Paschke R. Association of interleukin-6, C-reactive protein, interleukin-10 and adiponectin plasma concentrations with measures of obesity, insulin sensitivity and glucose metabolism. *Exp Clin Endocrinol Diabetes*. 2005;113:534-7.
5. Yuan G, Zhou L, Tang J, et al. Serum CRP levels are equally elevated in newly diagnosed type 2 diabetes and impaired glucose tolerance and related to adiponectin levels and insulin sensitivity. *Diabetes Res Clin Pract*. 2006;72:244-50.
6. Putz DM, Goldner WS, Bar RS, Haynes WG, Sivitz WI. Adiponectin and C-reactive protein in obesity, type 2 diabetes, and monodrug therapy. *Metabolism*. 2004;53:1454-61.
7. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation*. 2001;104:2886-91.
8. Tsang TS, Barnes ME, Bailey KR, et al. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. *Mayo Clin Proc*. 2001;76:467-75.
9. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455-61.
10. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946-52.
11. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med*. 1995;98:476-84.
12. Aksnes TA, Schmieder RE, Kjeldsen SE, Ghani S, Hua TA, Julius S. Impact of new-onset diabetes mellitus on development of atrial fibrillation and heart failure in high-risk hypertension (from the VALUE Trial). *Am J Cardiol*. 2008;101:634-8.
13. Nichols GA, Reinier K, Chugh SS. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. *Diabetes Care*. 2009;32:1851-6.
14. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271:840-4.
15. Johansen OE, Brustad E, Enger S, Tveit A. Prevalence of abnormal glucose metabolism in atrial fibrillation: a case control study in 75-year old subjects. *Cardiovasc Diabetol*. 2008;7:28.
16. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *Int J Cardiol*. 2005;105:315-18.
17. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart*. 2001;86:516-21.
18. Watanabe H, Tanabe N, Watanabe T, et al. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. *Circulation*. 2008;117:1255-60.
19. Iguchi Y, Kimura K, Aoki J, et al. Prevalence of atrial fibrillation in community-dwelling Japanese aged 40 years or older in Japan: analysis of 41, 436 non-employee residents in Kurashiki-city. *Circ J*. 2008;72:909-13.
20. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Med*. 2005;118:489-95.
21. Ostgren CJ, Merlo J, Rastam L, Lindblad U. Atrial fibrillation and its association with type 2 diabetes and hypertension in a Swedish community. *Diabetes Obes Metabol*. 2004;6:367-74.
22. Ruigómez A, Johansson S, Wallander MA, Garcia Rodriguez LA. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. *BMC Cardiovasc Disord*. 2005;5:20.
23. Ruigómez A, Johansson S, Wallander MA, Garcia Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. *J Clin Epidemiol*. 2002;55:358-63.
24. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. *J Intern Med*. 2001;250:382-9.
25. Jeong JH. Prevalence of and risk factors for atrial fibrillation in Korean adults older than 40 years. *J Korean Med Sci*. 2005;20:26-30.
26. Smith JG, Platonov PG, Hedblad B, Engström G, Melander O. Atrial fibrillation in the Malmö Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity. *Eur J Epidemiol*. 2010;25:95-102.
27. Zhou Z, Hu D. An epidemiological study on the prevalence of atrial fibrillation in the Chinese population of mainland China. *J Epidemiol*. 2008;18:209-16.
28. Dublin S, French B, Glazer NL, et al. Risk of new-onset atrial fibrillation in relation to body mass index. *Arch Intern Med*. 2006;166:2322-8.
29. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004;292:2471-7.
30. Heckbert SR, Wiggins KL, Glazer NL, et al. Antihypertensive treatment with ACE inhibitors or beta-blockers and risk of incident atrial fibrillation in a general hypertensive population. *Am J Hypertens*. 2009;22:538-44.
31. Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med*. 1994;154:1333-9.
32. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA*. 1995;274:620-5.
33. Smith NL, Heckbert SR, Lemaitre RN, et al. Esterified estrogens and conjugated equine estrogens and the risk of venous thrombosis. *JAMA*. 2004;292:1581-7.
34. Saunders KW, Davis RL, Stergachis A, Group Health Cooperative. In: Strom BL, ed. *Pharmacoepidemiology*. 4th ed. Chichester: John Wiley & Sons; 2005:234.
35. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol*. 2006;48:854-906.
36. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii, 1-253.
37. Lip GY, Varughese GI. Diabetes mellitus and atrial fibrillation: Perspectives on epidemiological and pathophysiological links. *Int J Cardiol*. 2005;105:319-21.
38. Otake H, Suzuki H, Honda T, Maruyama Y. Influences of autonomic nervous system on atrial arrhythmogenic substrates and the incidence of atrial fibrillation in diabetic heart. *Int Heart J*. 2009;50:627-41.
39. West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax*. 2006;61:945-50.
40. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol*. 2007;49:565-71.