Relation of Diabetes Mellitus to Incident Dementia in Patients With Atrial Fibrillation (from the Atherosclerosis Risk in Communities Study)

Ashwini Jiayaspathi, MBBS, MPH[a], Lin Yee Chen, MD, MS[b], Elizabeth Selvin, PhD[c], Rebecca F. Gottesman, MD, PhD[d], David S. Knopman, MD[e], Thomas H. Mosley, PhD[f], Faye L. Norby, PhD, MPH[g], and Alvaro Alonso, MD, PhD[a,*]

The association of diabetes mellitus (DM), an established risk factor for dementia in the general population, with incident dementia in patients with atrial fibrillation (AF) has not been explored. We performed a cohort study where we identified subjects with incident AF in the Atherosclerosis Risk in Communities cohort (1987 to 2017) and determined their DM status, fasting blood glucose before AF diagnosis and hemoglobin A1c levels using information from the closest previous study visit. Incident dementia was expert adjudicated using information from cognitive assessments, informant interviews and hospitalization surveillance. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia for each level of exposure using Cox models and adjusting for potential confounders. We analyzed 3,020 patients with AF in the Atherosclerosis Risk in Communities cohort (808 with DM) and 530 had incident dementia after a mean follow-up of 5.3 years after AF diagnosis. After multivariable adjustment, patients with AF with prevalent DM had higher rates of dementia than those without DM, HR 1.45 (95% CI 1.16 to 1.80). A value of hemoglobin A1c ≥6.5% was associated with a HR 1.29 (95% CI 0.97 to 1.71) of dementia. However, fasting blood glucose was not associated with rates of dementia independent of DM status. In conclusion, DM was associated with higher rates of dementia in patients with AF. DM prevention and control could be a promising avenue for reducing risk of dementia in AF. **(Am J Cardiol 2022;165:51−57)**

[a]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia; [b]Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota; [c]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [d]Stroke Branch, National Institute of Neurological Disorders and Stroke Intramural Research Program, National Institutes of Health, Bethesda, Maryland; [e]Department of Neurology, Mayo Clinic, Rochester, Minnesota; [f]Department of Medicine, University of Mississippi Medical Center, Jackson, Missouri; and [g]Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Heart System, Los Angeles, California. Manuscript received August 31, 2021; revised manuscript received and accepted November 1, 2021.

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*Corresponding author: Tel: +1 404 727 8714.

E-mail address: alvaro.alonso@emory.edu (A. Alonso).

Dementia is characterized by the deterioration of memory, thinking, behavior, and the ability to perform day to day activities. It has been estimated that 6.2 million Americans >65 years of age have Alzheimer's disease, the most common form of dementia, and it has been projected that these numbers may increase to 13.8 million by 2060.[1] Diabetes mellitus (DM) is a major lifestyle-associated chronic disease which is approaching enormous proportions globally. The International Diabetes Federation has estimated that the prevalence of DM is 9.3% globally, with the number of patients with DM worldwide likely to increase from 463 million in 2019 to 700 million by 2045.[2] Atrial fibrillation (AF), a common arrhythmia, is associated with increased risk of dementia, even in the absence of associated stroke.[3] Although studies have been conducted demonstrating the association between midlife cardiovascular risk factors like DM with the development of dementia later in life,[4] evidence of the role of DM as a risk factor for dementia in patients with AF is lacking. To address these knowledge gaps, we evaluated the association of DM, fasting blood glucose, and hemoglobin A1c (HbA1c), a marker of glycemic control, with the incidence of dementia among patients newly diagnosed with AF in a community-based cohort study.

Methods

The study population for this analysis was selected from the Atherosclerosis Risk in Communities Study (ARIC)

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cohort. ARIC is a prospective cohort study that recruited 15,792 men and women aged 45 to 64 years at baseline in 4 US communities (Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis suburbs, Minnesota; Washington County, Maryland). The study had a total of 6 visits in addition to baseline (1987 to 1989): 1990 to 1992, 1993 to 1995, 1996 to 1998, 2011 to 2013, 2016 to 2017, and 2017 to 2019. Details about study design and methods have been published elsewhere.[5] The ARIC study has been approved by institutional review boards of all participating institutions. Participants provided written informed consent at baseline and at each follow-up study visit.

We restricted our analyses to participants who developed incident AF during follow-up through 2017 or the latest available year and without dementia at the time of AF diagnosis. AF was ascertained in this cohort through 3 sources: study electrocardiogram (ECGs), hospital discharge codes, and death certificates. ECGs were performed during the study examinations using MAC PC Personal Cardiographs (Marquette Electronics, Milwaukee, Wisconsin) where a standard supine 12-lead ECG at rest was performed after 12-hour fast followed by a light snack and at least 1 hour after smoking tobacco or ingestion of caffeine. These ECGs were processed by the EPICARE center (Wake Forest University, Winston-Salem, North Carolina). Visual inspection of the ECGs was performed to assess the quality and look for technical errors.[6] In addition, trained abstractors obtained and recorded all hospital discharge diagnoses using International Classification of Diseases, Ninth Revision, Clinical Modification or International Classification of Diseases, Tenth Revision, Clinical Modification codes. AF was defined as International Classification of Diseases, Ninth Revision, Clinical Modification codes 427.31 or 427.32 and, starting in October 2015, International Classification of Diseases, Tenth Revision, Clinical Modification codes I48x, not occurring in the context of open-heart surgery. A validation study showed a positive predictive value of 89% with a sensitivity of 84% and a specificity of 98% for this method of AF ascertainment.[7] Our analysis excluded Asian, Native American, and Black participants from Minneapolis and Washington County because of very small numbers. Ultimately, the baseline population for our study consisted of 3,020 participants with AF.

The primary exposure of interest is prevalent DM (yes/no) at the time of AF diagnosis, using the variables from the visit before, or at the same time as, AF diagnosis. DM was defined in all visits as fasting blood glucose levels ≥126 mg/dl, nonfasting blood glucose levels ≥200 mg/dl, self-reported physician diagnosis of DM or self-reported use of antidiabetic medications.

For secondary analyses, we considered fasting blood glucose concentrations measured at all study visits and HbA1c measured at visits 2 (1990 to 1992) and 5 (2011 to 2013) (not available in other visits) as additional exposures. Serum glucose in the ARIC cohort was measured using the hexokinase method.[8] HbA1c was measured in whole blood samples maintained at −80°C using high-performance liquid chromatography using instruments that were standardized to the Diabetes Control and Complications Trial assay.[8] We used the most recent values of fasting blood glucose and HbA1c before AF diagnosis for the analysis.

The primary outcome of interest was incident dementia defined according to standard ARIC procedures after expert adjudication.[9] There were several approaches used to ascertain dementia. First, ARIC participants taking part in visits 5 and 6 (2011 to 2013, 2016 to 217) underwent a detailed assessment of neurocognitive function. A subset of these participants was selected to receive a neurologic examination and a magnetic resonance imaging of the brain. Second, a validated phone-based cognitive assessment, the modified version of the Telephone Interview for Cognitive Status (TICSm), was administered to participants who were alive at the time of visit 5 but unable or unwilling to participate in an in-person examination. When the participants were deceased or unable to complete the TICSm by themselves, informants provided additional information using the Clinical Dementia Rating and Functional Activities Questionnaire. Finally, in the full cohort, hospitalization codes were used to identify incident dementia occurring from visit 1 to end of visit 6. For our analysis, we considered cases of dementia identified through any of these sources. The date of dementia diagnosis was defined depending on the source of dementia diagnosis. In participants identified through in-person cognitive evaluations, the date of assessment was used as the date of dementia diagnosis, with an exception of using the hospitalization dates in those with a previous dementia hospitalization. The earliest date from TICSm, informant interview, or hospitalization discharge, as applicable, was used for study participants with dementia diagnosis from other sources. To account for the lag in determining dementia identified by interviews, deaths, and hospitalization, 6 months were subtracted from the dates to identify the date of dementia onset.[4] In study participants who were never diagnosed with dementia, the earliest of the date of visit 6 examination, date of loss to follow-up, December 31, 2017, or the date of death was used to calculate the follow-up time.

Covariates used in our analysis included participant demographics, co-morbidities, and use of certain medications ascertained at study visits or the time of AF diagnosis. The demographic information included self-reported age (at time of AF diagnosis), gender, race (White, Black), study site (Forsyth County, Jackson, Minneapolis suburbs, Washington County), education level (basic, intermediate, high), and smoking and alcohol drinker status (current, former, never, missing). Because visit center and the race of participants were correlated, we categorized participants jointly by race and center (White participants from Forsyth County, White participants from Minneapolis, White participants from Washington county, Black participants from Forsyth County, and Black participants from Jackson).

Heart failure, stroke and myocardial infarction incidence were defined according to criteria described elsewhere.[10–12] Total cholesterol was measured at all visits using standard procedures. The use of blood pressure-lowering medications, anticoagulants, statins, and aspirin were ascertained by self-report at all visits. Systolic and diastolic blood pressures were measured 3 times and the mean of the second and third measurements were used for analysis. However, in visit 4, blood pressure was only measured twice and the mean of these 2 values were used. Genotyping for *APOE* polymorphisms in ARIC cohort were performed using the TaqMan

assay, where variants on the codons 130 and 176 were assayed separately. The data obtained from these codons were then combined to generate the 6 *APOE* genotypes: 22, 23, 33 (used as reference), 24, 34, and 44.[13]

SAS 9.4 (SAS Institute Inc., Cary, North Carolina) and Stata 16.1 (Stata Corp. LLC, College Station, Texas) were used for statistical analysis. DM status in study participants was defined with respect to the date of diagnosis of AF. Means and SDs were calculated for continuous variables, and frequencies and percentages for categoric variables by DM status. Time-to-event was calculated as the time from AF diagnosis to time of dementia diagnosis or censoring (death, lost to follow-up, visit 6 date, or December 31, 2017). We calculated crude incidence rates of dementia in participants with and without DM, and the corresponding incidence rate ratio (participants without DM as the reference). Cumulative incidence curves were generated for the association between DM and dementia before and after accounting for the competing risk of death.

We assessed the association between DM diagnosis and incidence of dementia among ARIC participants with AF using Cox regression to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). In model 1, we adjusted for demographics (age, gender, and race/center). In model 2, we additionally adjusted for education, smoking, drinking, anticoagulant use, aspirin use, antihypertensive use, statin use, myocardial infarction, stroke, prevalent heart failure, body mass index, total cholesterol, systolic blood pressure, diastolic blood pressure, and *APOE* genotype. Effect measure modification by age (<74, ≥74 years), gender (male, female), and race was assessed after adjusting for model 2 covariates. We repeated the analysis using a Fine-Gray subdistribution hazard model considering death as a competing risk and calculating subdistribution HR (SHR) and their 95% CIs.[14]

Secondary analysis was performed using glucose tertile cut points as the exposure of interest. These cut points were created separately in participants with and without DM, and the lowest tertile among participants without DM were used as the reference category. We assessed the association between DM-specific glucose tertiles and diagnosis of dementia using Cox regression. An additional secondary analysis was performed using HbA1c as the exposure of interest, using a HbA1c value of 6.5% as the cut point. As with the primary analysis, we performed an initial analysis adjusting for demographic variables (model 1) followed by a model adjusting for multiple covariates (model 2). DM status was not included as a covariate in the model. We also explored effect measure modification by age, gender, and race/center as described previously.[15]

Results

Of the 15,792 participants of the ARIC cohort, we included 3,020 eligible subjects in the final analysis. At the time of AF diagnosis, 808 participants (27%) had a diagnosis of DM. Use of antihypertensives, heart failure prevalence, and mean body mass index were higher in participants with DM compared with those without DM. The racial and gender distribution was similar between the 2 groups (Table 1).

Table 1
Characteristics of patients with atrial fibrillation according to their diabetes status at time of atrial fibrillation diagnosis, ARIC 1987-2017

Variable, N= 3020	Diabetes mellitus	
	Yes (n = 808)	No (n = 2212)
Age (years)	73 ± 8	74 ± 8
Male	407 (50%)	1151 (52%)
Female	401 (50%)	1061 (48%)
Black	212 (27%)	316 (14%)
White	596 (74%)	1896 (86%)
Education level		
None of the mentioned categories	4 (0.5%)	1 (0.1%)
Basic education or 0 years education	253 (31%)	504 (23%)
Intermediate education	333 (41%)	932 (42%)
Advanced education	218 (27%)	775 (35%)
Smoker		
Current	128 (16%)	431 (20%)
Former	388 (48%)	1006 (46%)
Never	273 (34%)	742 (34%)
Unknown	19 (2.4%)	33 (1.5%)
Alcohol drinking status		
Current	302 (37%)	1164 (53%)
Former	302 (37%)	636 (29%)
Never	204 (25%)	411 (19%)
Unknown	0 (0%)	1 (0.1%)
Aspirin use	522 (65%)	1390 (63%)
Antihypertensive use	645 (80%)	1245 (56%)
Anticoagulant use	49 (6.1%)	113 (5.1%)
Statin use	237 (29%)	394 (18%)
Total cholesterol (mmol/L)	5.0 ± 1.2	5.1 ± 1.0
Body mass index (kg/m^2)	32.4 ± 6.3	28.7 ± 5.9
Systolic blood pressure (mmHg)	134 ± 23	131 ± 21
Diastolic blood pressure (mmHg)	69 ± 12	71 ± 12
APOE ε4 allele	211 (26%)	605 (27%)
History of myocardial infarction	176 (22%)	265 (12%)
Prevalent CHD	205 (25%)	329 (15%)
Prevalent stroke	42 (5.2%)	73 (3.3%)
Prevalent heart failure	327 (41%)	613 (28%)

Values correspond to mean ± standard deviation or n (%).

There were 530 patients with incident dementia. Unadjusted incidence rates of dementia in participants with and without DM were 4.5 (95% CI 3.7 to 5.3) and 3.1 (95% CI 2.8 to 3.4) per 100 person-years, respectively (incidence rate ratio 1.5, 95% CI 1.2 to 1.8) (Table 2).

Unadjusted Kaplan−Meier curves showed an increased risk of dementia in participants with DM compared with participants without DM (Figure 1). Unadjusted cumulative incidence function curves accounting for the competing risk of death showed a cumulative incidence of dementia in patients with DM not different from those without DM (Figure 2).

The hazard of incident dementia among those with DM was found to be 58% (HR 1.58, 95% CI 1.29 to 1.93) higher than the hazard of incident dementia among those without DM after adjustment for demographic variables. A model adjusting for additional covariates also demonstrated an increased hazard of incident dementia among those with DM (HR 1.45, 95% CI 1.16 to 1.81) compared with those without DM (Table 3). In a competing risks analysis using a Fine-Gray subdistribution hazard regression model, accounting for the competing risk of death, DM was not

Table 2
Crude incidence rates and incidence rate ratios of dementia by diabetes status among participants with AF, ARIC 1987-2017

N	No diabetes	Diabetes
Incident dementia, n	393	137
Person-years	12,768	3,075
Incidence rate (95%CI)*	3.1 (2.8, 3.4)	4.5 (3.7, 5.3)
Incidence rate ratio (95%CI)	1 (ref.)	1.45 (1.19, 1.76)

* Per 100 person-years.

associated with dementia in AF patients (SHR 1.02, 95% CI 0.81 to 1.28, in a multivariable model) (Table 4). Finally, we assessed effect measure modification by age, gender, and race of the study participants and did not find any evidence of heterogeneity by these variables (Supplementary Table 1).

Fasting blood glucose was categorized in 6 groups, 3 among patients with DM and 3 among those without DM, using DM-specific tertiles in blood glucose distribution from the closest study visit before AF diagnosis. The lowest category among those without DM with a fasting blood glucose value of <96 mg/dl was considered to be the reference for the Cox models. In the baseline model, the hazard for incident dementia was statistically significantly higher among all those with DM, independent of their blood glucose levels. After adjusting for additional covariates, there was a statistically significant association between fasting blood glucose and incidence of dementia only among participants with DM with fasting blood glucose <131 mg/dl with a HR of 1.74 (1.20 to 2.52), with nonsignificant increased risk in those with DM and higher glucose levels (Table 3). We did not find evidence of heterogeneity in these associations by age, gender, or race (Supplementary Table 2).

Using a cut off for HbA1c of 6.5%, in the baseline model, there was a 45% (HR 1.45, 95% CI 1.12 to 1.89) increased hazard of incident dementia among those with HbA1c values ≥6.5% compared with those with HbA1c <6.5%, based on measurements from the closest previous study visit. After adjusting for all other covariates in the baseline model the association was attenuated, with a 29% (HR 1.29, 95% CI 0.97 to 1.71) increased hazard of incident dementia among those with HbA1c values ≥6.5% (Table 3). There was no evidence of effect measure modification in these associations by age, gender, or race (Supplementary Table 3).

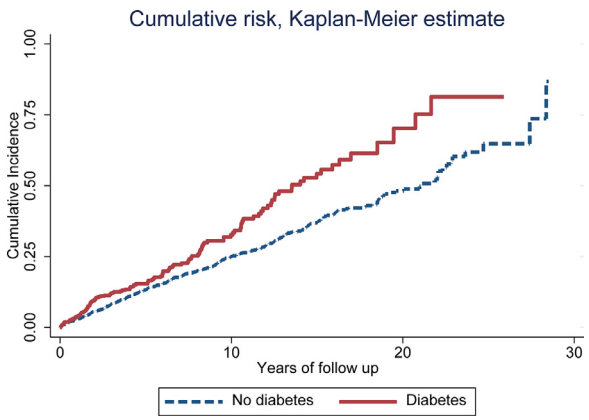

Figure 1. Unadjusted cumulative incidence of dementia in atrial fibrillation patients by diabetes status, Kaplan−Meier estimates, ARIC 1987 to 2017.

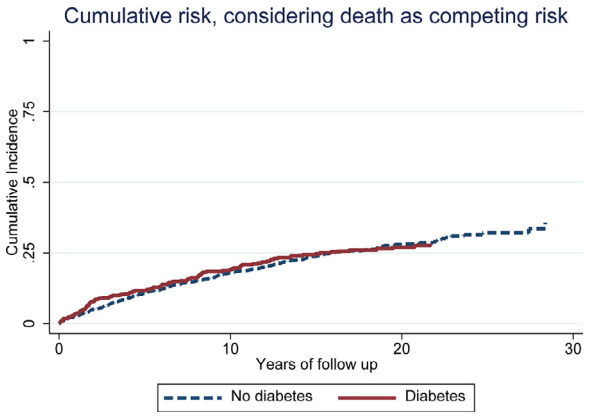

Figure 2. Unadjusted cumulative incidence of dementia in atrial fibrillation patients by diabetes status accounting for competing risk of death, ARIC 1987 to 2017.

Table 3
Hazard ratios and 95% confidence intervals of incident dementia for the 3 different exposures: diabetes (primary analysis), blood glucose levels (secondary analysis), HbA1c levels (secondary analysis), ARIC 1987-2017

Primary analysis			
Diabetes	HR	95% CI	P value
Model 1*	1.58	1.29, 1.93	<0.0001
Model 2†	1.45	1.16, 1.81	0.0009
Secondary analysis: glucose levels			
Model 1*			
Glucose levels	HR	95% CI	P value
0 (<96mg/dl & D=0)	Reference	Reference	Reference
1 (96 to <105 mg/dl & D=0	1.02	0.8, 1.31	0.86
2 (≥105 mg/dl & D=0)	1.05	0.81, 1.35	0.72
3 (<131 mg/dl & D=1)	1.99	1.42, 2.79	<0.0001
4 (131 to <171 mg/dl & D=1)	1.41	1.01, 1.96	0.04
5 (≥171 mg/dl & D=1)	1.54	1.05, 2.27	0.03
Model 2†			
0 (<96mg/dl & D=0)	Reference	Reference	Reference
1 (96 to <105 mg/dl & D=0	0.99	0.77, 1.29	0.95
2 (≥105 mg/dl & D=0)	0.97	0.74, 1.27	0.83
3 (<131 mg/dl & D=1)	1.74	1.20, 2.52	0.004
4 (131 to <171 mg/dl & D=1)	1.30	0.91, 1.86	0.15
5 (≥171 mg/dl & D=1)	1.31	0.87, 1.97	0.20
Secondary analysis: HBA1C			
HBA1C (≥6.5% vs. <6.5%)	HR	95% CI	P value
Model 1*	1.45	1.12, 1.89	0.005
Model 2†	1.29	0.97, 1.71	0.08

* Model 1: Adjusted for age, sex and race/center.
† Model 2: Additionally, adjusted for education, smoking status, drinking status, total cholesterol, body mass index, systolic blood pressure, diastolic blood pressure, H/O of myocardial infarction, prevalent CHD, prevalent stroke, incident heart failure, incident stroke, antihypertensive use, anticoagulant use, statin use and *APOE* genotype.

Table 4
Side by side comparison of the Cox proportional hazards model with the sub-distributional hazard's regression model (primary analysis: exposure diabetes), ARIC 1987-2017

Cox proportional hazards model			
Diabetes	HR	95% CI	P value
Model 1*	1.58	1.29, 1.93	<0.0001
Model 2†	1.45	1.16, 1.81	0.0009
Fine gray sub distribution hazard model			
Diabetes	SHR	95% CI	P value
Model 1*	1.01	0.82, 1.24	0.91
Model 2†	1.02	0.81, 1.28	0.86

* Model 1: Adjusted for age, sex and race/center.
† Model 2: Additionally, adjusted for education, smoking status, drinking status, total cholesterol, body mass index, systolic blood pressure, diastolic blood pressure, H/O of myocardial infarction, prevalent CHD, prevalent stroke, incident heart failure, incident stroke, antihypertensive use, anticoagulant use, statin use and *APOE* genotype.

Discussion

In this analysis of a large community-based cohort, we found that among subjects with underlying AF, a diagnosis of DM was associated with higher rates of incident dementia compared with those who did not have DM. Analyses of the effects of levels of fasting blood and long-term blood sugar control on incident dementia did not show an association with increased rates of dementia, independent of DM status. The associations were similar among White and Black participants, and men and women; and did not vary based on age, although this observation should be interpreted in the context of limited sample size. The associations persisted even after adjusting for confounders in the baseline model.

Our findings suggest that (1) a diagnosis of DM was independently associated with an increased hazard of dementia in patients with underlying AF after adjusting for all covariates; (2) however, upon accounting for the competing risk of death in this population, dementia risk among patients with DM was similar to that among patients without DM.

Growing evidence demonstrates that DM is a risk factor for dementia and cognitive decline. A previous study conducted in the ARIC cohort reported an increased risk of dementia hospitalization in those with DM (HR 2.2, 95% CI 1.6 to 3.0).[13] Also in the ARIC cohort, DM in midlife was associated with a 19% greater cognitive decline over 20 years compared with no DM.[16] Whether DM is risk factor for dementia in patients with AF has not been specifically assessed. This question is relevant because the mechanisms underlying dementia development in AF are not completely elucidated.

The main mechanisms through which DM-induced hyperglycemia may lead to dementia include inflammation, mitochondrial dysfunction, and oxidative stress.[17] These in turn lead to development of brain insulin resistance (caused by hyperglycemia and hyperinsulinemia) and amyloidogenesis, which contributes to the neuropathologic manifestations of impaired neuronal integrity and neurodegeneration, eventually causing impaired cognitive functioning.[17] These processes eventually result in an overall increased risk of dementia among patients with DM. Patients with underlying AF also tend to have an increased risk of dementia and cognitive impairment because of increased stroke risk, cerebral hypoperfusion, vascular inflammation, cerebral small vessel disease, and brain atrophy.[18] Thus, inflammation is an underlying mechanism for dementia in both DM and AF. Hence, having DM with AF can put a patient at an increased risk of developing cognitive impairment and dementia. The association of diabetes with dementia in patients with AF may also apply to patients who have signs of atrial cardiopathy, such as advanced interatrial block.

Upon conducting a Fine-Gray subdistribution hazards regression which accounts for the competing risk of death, we found that DM was no longer associated with dementia risk in this sample. This can be attributed to the increased risk of death in patients with DM, particularly at an older age. Thus, participants with DM present an overall cumulative risk of dementia that is lower than if the competing risk of death was not present; this reduction is stronger than in those without DM, leading to a SHR close to 1. Given the differences between the HR from the standard Cox proportional hazards model and the SHR from the subdistribution hazards model, we decided to present both.[19] However, the final decision on which model to utilize depends on the aim of the research study. Although using the Fine-Gray model with the subdistribution hazard can be useful in prognostic studies,[14] epidemiologic cohort studies conducted to identify etiologic associations in the presence of competing risk should use the standard Cox proportional hazards model. In this particular case, the results show that DM is associated with an increased hazard of dementia but the cumulative risk of dementia in those with and without DM is similar.[20] When competing risks are present, the assumption of independence between censoring and the outcome is violated because patients censored because of the competing risk are no longer at risk of the outcome. Therefore, in prognostic studies, ignoring the fact that a subject dies before developing the outcome actually overestimates cumulative risk.[21] However, etiologic studies, in which we are interested in determining whether those exposed to a particular risk factor have an increased risk of developing the disease at a particular time, do not require consideration of competing risks as long as predictors of the competing risk are included in the model as covariates.[20,22]

Some limitations of the present analysis need to be mentioned. First, the information on HbA1c was available only from visits 2 and 5. Similarly, fasting blood glucose measurements were available only at study visits, not necessarily at the time of AF diagnosis. This lag between exposure assessment and AF diagnosis results in misclassification, likely to be nondifferential and independent from the outcome. Second, the method used for AF ascertainment in the ARIC cohort may miss asymptomatic cases of AF and those managed exclusively in outpatient settings. Third, having information on medications taken by the study participants to control blood sugar would have been helpful because

they can be protective against cognitive decline. However, information regarding medications has not been collected in this cohort. Fifth, we also do not have information on the quality of anticoagulation control, like bleeding or clotting time, available in this cohort. Finally, using hospitalization codes as the sole source of incident dementia diagnosis for participants in which no other information was available posed the risk of having limited sensitivity.

In spite of the limitations mentioned previously, our study has certain strengths; the most important of which is the long follow-up period of 30 years from 1987 to 2017. Another major strength of this study was the large sample size with the presence of adequate number of events available to perform the analysis. Data completeness was an additional strength, given the lack of significant missing information on covariates considered and adjusted for (<5%). The availability of repeated measurements of glucose and HbA1c helped us ascertain the value closest to the time of AF diagnosis, providing a more accurate exposure status at baseline. Finally, the racially diverse study population also stands out as a major strength because previous studies conducted for determining dementia incidence were almost entirely Whites of European ancestry.[23] This helps us gain a better perspective about whether there are racial differences in the development of incident dementia.

In conclusion, our analysis of this large community-based cohort followed for almost 30 years, spanning a total of 6 in-person visits, provides evidence that a diagnosis of DM in patients with AF is associated with higher hazard of incident dementia compared with patients without DM. In addition, the association of DM with dementia was independent of fasting blood glucose levels. This information suggests that prevention of DM could lead to reduced rates of dementia in patients with AF and provides support to explore pathophysiologic mechanisms responsible for these elevated rates.

Disclosures

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Supplementary materials

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