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Impact of Intensive Glycemic Control on the Incidence of Atrial Fibrillation and Associated Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (from the ACCORD Study)

Omid Fatemi, MD^{1,2,3}, Eugene Yuriditsky, MD^{1,2,3}, Costas Tsioufis, MD⁴, Demetrios Tsachris, MD⁴, Timothy Morgan, MD⁵, Jan Basile, MD^{6,7}, Thomas Bigger, MD⁸, William Cushman, MD⁹, David Goff, MD PhD¹⁰, Elsayed Z. Soliman, MD⁵, Abraham Thomas, MD¹¹, and Vasilios Papademetriou, MD^{2,3}

¹Washington Hospital Center

²Georgetown University Hospital

³Washington DC Veteran's Medical Center

⁴Hippokration Hospital University of Athens, Greece

⁵Wake Forest Baptist Medical Center

⁶Medical University of South Carolina

⁷Ralph H Johnson VA Medical Center

⁸Columbia University Medical Center

⁹University of Tennessee Health Science Center

¹⁰Colorado School of Public Health

¹¹Henry Ford Health System

Abstract

Atrial fibrillation (AF) is prevalent among individuals with type 2 diabetes mellitus (DM), and is associated with markers of poor glycemic control; however the impact of glycemic control on incident AF and outcomes is unknown. We sought to prospectively evaluate if intensive glycemic control in individuals with DM impacts incident AF, and to evaluate morbidity and mortality among individuals with DM and incident AF. We studied 10,082 individuals with DM from the ACCORD cohort in a randomized, double-blind fashion. Participants were randomized to an intensive therapeutic strategy targeting a glycated hemoglobin level of <6.0%, or a standard strategy targeting a glycated hemoglobin of 7.0-7.9%. Incident AF occurred in 159 patients

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Corresponding Author: Eugene Yuriditsky, 1010 G. St. NE Apt 103, Washington, DC 20002, Tel: 410-963-6156
eugene.yuriditsky@gmail.com.

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(1.58%) over the follow-up period at a rate of 5.9/1,000 person-years in the intensive-therapy group, and a rate of 6.37/1,000 person-years in the standard-therapy group ($p=0.52$). In a multivariate model, predictors of incident AF were age, weight, diastolic blood pressure, heart rate, and heart failure history. Patients with DM and new-onset AF had a HR of 2.65 for all-cause mortality (95% CI 1.8-3.86, $p<0.0001$), HR of 2.1 for myocardial infarction (95% CI 1.33-3.31, $p=0.0015$), and HR of 3.80 for development of heart failure (95% CI 2.48-5.84, $p<0.0001$). In conclusion, intensive glycemic control did not impact rate of new-onset AF. Patients with DM and incident AF had an increased risk for morbidity and mortality as compared to those without AF.

Keywords

Arrhythmias; Atrial fibrillation; Diabetes

INTRODUCTION

Type 2 Diabetes mellitus (DM) confers roughly a 40% increased risk for developing AF as compared to individuals without DM (1-8). Excess cardiovascular morbidity and mortality are attributable to AF in individuals with DM (1, 9). In multiple studies, baseline AF was associated with a significantly greater risk for all-cause mortality and comparable higher risk for cardiovascular death, stroke, and heart failure (9); incident AF among individuals with DM leads to increased risk for stroke and heart failure (1). Risk for AF among individuals with DM has been linked to glycemic control (3,5,6). Among treated individuals with DM with new AF in a population-based case-control study, every 1% increase in HbA1c increased the risk for AF by 14% (3). In a large study, HbA1c and fasting glucose levels positively and independently correlated with incident AF among DM patients (5). Prospectively, a series of small clinical trials have demonstrated reduced incidence of perioperative AF among patients with DM undergoing coronary artery bypass grafting subjected to more stringent glycemic control (10, 11). Whether long-term glycemic control alters incident AF or outcomes in individuals with DM is unknown. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to address the impact of intensive glycemic control, as compared to standard treatment, on cardiovascular outcomes. Those in the intensive therapy arm had increased mortality and complication rates (12). In the present analysis, we examined the impact of intensive versus standard glycemic control on the incidence of AF, and evaluated the impact of AF on mortality and other cardiovascular events among patients with incident AF in the ACCORD trial (12).

METHODS

The rationale and design of the ACCORD trial have been previously described (12-14). Briefly, this was a National Heart, Lung, and Blood Institute (NHLBI) sponsored trial conducted in 77 clinical centers across the United States and Canada. Volunteers with DM, an HbA1c level of ≥ 7.5 , and an age of 40 to 79 were recruited. By inclusion criteria, subjects had either cardiovascular disease, or were between the ages of 55 and 79 and had anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional cardiovascular risk factors (dyslipidemia, hypertension, current smoking

status, or obesity). Those with either frequent or recent hypoglycemic events, a body-mass index exceeding 45 kg/m², serum creatinine of >1.5 mg/dL, serious illness, or unwillingness to participate in home glucose monitoring or insulin injection were excluded.

All 10,251 patients were randomly assigned to receive intensive therapy targeting a HbA1c level of <6.0%, or to receive standard therapy targeting an HbA1c of 7.0 to 7.9%. Regimens were individualized at the investigators' and patients' discretion with careful auditing of adverse responses to therapies. Patients in the intensive therapy group were followed monthly in the clinic for the first 4 months, then every 2 months thereafter with additional visits as necessary; patients in the standard therapy group attended visits every 4 months. The intensive glycemia intervention was stopped early owing to increased mortality in the glycemia control arm, and all participants were transitioned to the standard glycemia control intervention.

Twelve-lead electrocardiograms (ECGs) were obtained at the start of the trial and at the biennial follow-up visits (i.e., every 2 years) and close-out visit. In all ACCORD sites, ECGs were digitally acquired using a GE MAC 1200 electrocardiograph (GE, Milwaukee, Wisconsin) at 10 mm/mV calibration and a speed of 25 mm/s. ECG reading was performed centrally at the Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston Salem, North Carolina. All electrocardiograms were initially inspected visually for technical errors and inadequate quality before being automatically processed using GE 12-SL Marquette Version 2001 (GE, Milwaukee, Wisconsin). ECG abnormalities including atrial fibrillation were classified and coded using the Minnesota ECG Classification (15).

Adverse events included in our study were the pre-specified primary outcome (a composite of first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes), any myocardial infarction (MI), nonfatal MI, death from any cause, death from a cardiovascular cause, any stroke, nonfatal stroke, congestive heart failure (CHF), angina, or revascularization. Cardiovascular death included death from an MI, CHF, arrhythmia, invasive cardiovascular intervention, stroke, sudden cardiac death, and death from other vascular disease (12).

Baseline characteristics were compared in the two study groups with the use of chi-square tests and two-sample t-tests. Analyses of outcomes were performed with the use of time-to-event methods according to the intention-to-treat principle, and occurrences of these outcomes in the two study groups were compared with the use of hazard ratios and 95% confidence intervals. Two sided P values were obtained from likelihood ratio tests from Cox proportional-hazards regression analyses. New-onset AF rates are expressed as events per 1,000 person-years, taking into account censoring of follow-up data. Kaplan–Meier estimates were used to obtain the proportion of patients who developed AF during follow-up. The risks of events associated with the incidence of AF were estimated using Cox proportional hazards models, with adjustment for potential confounding baseline covariates which were thought to be of prognostic importance for the outcomes of interest. All statistical analyses were conducted at the coordinating center with the use of S-Plus software, version 8.0 (Insightful) or SAS software, version 9.1 (SAS Institute).

RESULTS

Of the 10,251 individuals enrolled in ACCORD, 10,209 had baseline ECG data available and of these patients, 10,082 without baseline AF were included in our analysis. Incident AF was diagnosed in 159 of the 10,082 participants (1.58%) by ECG at one of the follow-up visits over a median of 4.68 years. The mean age of the group was 62.2 years ($SD \pm 6.8$) with approximately 39% being female. The average HbA1c at baseline was 8.3%. The median HbA1c level achieved at 1 year, and maintained throughout the follow-up period, was 6.4% (IQ range 6.1-7.0) and 7.5% (IQ range 7.0-8.1) respectively (12). Baseline characteristics of the study groups were similar and are listed in Table 1.

New-onset AF occurred at a rate of 5.9 per 1,000 person-years in the intensive group and a rate of 6.37 per 1,000 person-years in the standard group ($p=0.52$). Univariate predictors of incident AF are listed in table 2. After stepwise regression analysis, remaining multivariate predictors were age, weight, diastolic blood pressure, heart rate, and previous heart failure with hazard ratios presented in Table 3. Among the entire cohort, AF was associated with a higher incidence of the primary outcome—first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular cause, all-cause mortality, cardiovascular death, any MI, nonfatal MI, and CHF. When stratified by study group, AF did not reach a significant association with myocardial infarction or nonfatal myocardial infarction in the standard-therapy group; however, this association remained in the intensive-therapy group. AF was not associated with stroke, nonfatal stroke, angina, or revascularization (Figure 1).

DISCUSSION

In the present study we assessed, in a randomized fashion, the impact of intensive versus standard glycemic control on the incidence of AF, as detected by periodic ECG monitoring, among high-risk individuals with DM, as well as the prognostic value of incident AF in this population. We demonstrated a lack of association between intensive versus standard glycemic control and incident AF; however, individuals with DM with AF detected by periodic ECG monitoring were at increased risk for morbidity and mortality, excluding stroke events.

In an observational cohort, Nichols *et al.* reported the incidence rate of AF in a population of 10,213 DM patients of 9.1 per 1,000 person-years (95% CI 8.6-9.7) over a 7.2 ± 2.8 year follow-up period compared to 6.6 per 1,000 person-years in the control population (95% CI 6.2-7.1) (16). The reported incidence is lower in our study, by contrast to Nichols *et al.*, as we did not solicit all electronic medical records of patient encounters and therefore may have been more likely to miss some occurrences of AF (16).

In our study, intensive glycemic control did not affect incident AF in a high-risk population with DM. This is the first prospective randomized trial to address this question. Two prior studies linked glycemic indices to incident AF in individuals with DM (3, 4). In a population-based case-control study, Dublin *et al.*, found a 14% increased risk for incident AF among treated patients for every 1% increase in HbA1c (3). However, Dublin *et al.* did not address AF risk based on treatment intensity. In the Atherosclerosis Risk in

Communities (ARIC) cohort, Huxley *et al.* (5) found HbA1c levels positively and independently correlated with incident AF in patients with and without DM; among individuals with DM, there was a significant linear association between fasting blood glucose and risk for incident AF (5). Treatment effect targeting HbA1c was not addressed in this study suggesting HbA1c may merely be a marker of elevated risk.

Demographic factors including older age, Caucasian race, male gender, and heavier weight were associated with increased risk for AF in our study, and are consistent with previous findings (4, 17, 18). In the Framingham study, men were at a 1.5 times greater risk for developing AF than women (19). We found men were 1.2 times more likely to develop AF with some difference likely related to the study population. In a study examining pooled data from 3 cohorts of individuals with significant risk factors, AF was more prevalent in Caucasians (5%) as compared to African Americans (1%) (17). Similar racial differences were noted in our study. Obesity is a known risk factor for AF independent of other co-morbidities. In the Framingham study, a 4% increased risk for AF was observed per 1-unit increased in BMI. However, the association between BMI and AF risk was no longer significant after adjustment for left atrial diameter (20). Hypertension is a known risk factor for AF; Among the ARIC cohort, hypertension was the most potent predictor of AF explaining nearly one fifth of all cases (4, 18). The discrepant finding in our study may reflect that hypertensive patients are undergoing treatment; management of their hypertension may not mitigate the risk for AF.

Pathophysiologic links between DM and AF include autonomic, electrical, and structural remodeling, as well as insulin resistance. Such factors lead to increased oxidative stress, changes in sympathetic activity, and alterations in myocardial electrical properties (21, 22). Furthermore, DM is associated with a cardiomyopathy unrelated to underlying hypertension that is characterized by cellular and electrical changes within the myocardium. Hypoglycemic episodes and glycemic fluctuations have also been associated with an increased frequency of AF among individuals with DM (6, 23).

Detrimental effects of glycemic fluctuations may have offset theoretical advantages of intensive glycemic control for AF incidence –a known association with AF (6, 24, 25). Hypoglycemia induces sympathetic activation, leads to catecholamine surge, increases cardiac workload, and induces ECG changes; numerous case reports demonstrate hypoglycemia-associated AF (24). Further, markers of inflammation such as high-sensitivity C-reactive protein and interleukin 6 are increased in acute hypoglycemia and are linked to the initiation and perpetuation of AF (25-27). Fluid retention, which occurred more frequently in the intensive-therapy control group, is a known predisposing risk factor for AF via mechanism of renin-angiotensin-aldosterone system activation, and increased atrial stretch (28).

After multivariate adjustment, individuals with DM with new-onset AF were at significantly higher risk for adverse outcomes including death, myocardial infarction, and heart failure, as compared to individuals without AF. The risk for stroke however, was not higher in this population. AF independently confers elevated risk for adverse events in patients with DM. In the Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled

Evaluation (ADVANCE) study, patients with DM with known AF were at increased risk for death, cardiovascular death, heart failure, and major cerebrovascular events as compared to those without AF (9).

Atrial fibrillation is a known independent risk factor for stroke (9, 19). That in our adjusted model new AF did not result in excess stroke risk is therefore surprising. Although our study was not powered to detect this difference, there are multiple potential explanations to this finding. As we only obtained ECGs at periodic clinic visits, cases of AF were likely to have been under-diagnosed. Further, as we only excluded patients without baseline AF on screening ECG, it is conceivable that patients may not have been truly free of AF at baseline. As we did not collect data on inpatient admissions and emergency department visits, we may have under-estimated AF burden in the two groups.

Intensive-therapy did not improve morbidity or mortality among diabetics with new-onset AF but the study was not powered to detect such a difference. These findings are concordant with those of the ACCORD trial (12). In fact, intensive therapy significantly increased the risk for primary outcome, all-cause mortality, cardiovascular death, and any or nonfatal myocardial infarction. The aforementioned complications related to intensive-therapy (frequency of hypoglycemic episodes, fluid retention, and increased use of medications of different classes) may account for this finding.

Our study's main limitation lies in the methodology of detecting incident AF. The use of periodic ECG recordings obtained at clinic visits, as compared to the use of event monitors, or inpatient record review, potentially lead to missed episodes of AF and therefore created a bias toward the null hypothesis. We did not have a way of accounting for those who underwent cardioversions or other rhythm- control strategies; these individuals would be labeled as not having AF on follow-up ECGs. Our data does not report the drop-out rate by group with regard to clinic visit attendance and ECG obtainment. As a result, we may have included some patients who did in fact have a form of AF at baseline while missing episode during follow-up. As we did not have information on the use of anticoagulant agents in the cohort, it is not possible to draw conclusions concerning stroke risk in these groups; potentially patients may have been diagnosed with AF during an inpatient admission and started on anticoagulant therapy decreasing stroke risk.

Our study focused individuals with DM subject to an intensive glycemic control strategy versus a standard glycemic control strategy which limits our ability to make conclusions about incident AF among individuals with poor glycemic control versus those subject to a standard glycemic control strategy. It is therefore not possible to conclude that any degree of glycemic control has no impact on incident AF. Our data may not be generalizable to patients with DM as a whole as our population only included "high-risk" individuals with DM.

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Research Highlights

- Intensive glycemic control did not alter the rate of incident atrial fibrillation
- We describe a number of predictors of atrial fibrillation among individuals with diabetes
- Incident atrial fibrillation is associated with adverse outcomes among individuals with diabetes

Figure 1. Relationship between new onset AF and outcomes presented with hazard ratios (HR) and 95% confidence intervals (CI).

Table 1

Baseline patient characteristics presented as means with standard deviation or percent.

Characteristic	Standard (N = 5042)	Intensive (N = 5040)	P-value
Age (years)	62.2 ±6.8	62.2 ±6.8	0.94
Female sex	38.6%	38.8%	0.87
White	64.9%	64.1%	0.40
Black	19.0%	19.9%	0.27
Hispanics	7.5%	7.0%	0.33
Weight (kgs)	93.5 ±15.6	93.4 ±18.6	0.86
Waist (cm)	106.7 ±13.7	106.7 ±14.0	0.81
Body mass index (kg/m ²)	32.2 ±5.5	32.2 ±5.5	0.74
Smoking	13.7%	14.3%	0.45
Duration of DM (years)	10.9 ±7.8	10.8 ±7.8	0.58
ECG LV hypertrophy	5.2%	5.2%	0.99
Systolic blood pressure (mmHg)	136.5 ±17.2	136.3 ±17.0	0.49
Diastolic blood pressure (mmHg)	75.0 ±0.6	74.8 ±10.6	0.37
Pulse pressure (mmHg)	61.5 ±14.7	61.5 ±14.6	0.87
Heart rate (bpm)	72.5 ±11.7	72.7 ±11.7	0.38
Previous CV event	34.9%	35.5%	0.56
Previous heart failure	4.6%	4.6%	0.97
Medications			
Insulin	35.7%	34.0%	0.073
Metformin	60.2%	59.8%	0.70
Any sulfonylurea	49.4%	50.8%	0.17
Any antihypertensive agent	85.9%	84.7%	0.10
ACE-inhibitors	53.0%	52.8%	0.86
ARBs	16.4%	15.6%	0.29
Any thiazide diuretic	19.1%	19.5%	0.64
Beta-blockers	29.7%	28.4%	0.13
Alpha-beta blockers	2.8%	2.5%	0.42
Dihydropyridine CCBs	11.7%	11/6%	0.82
Non-dihydropyridine CCBs	7.3%	6.7%	0.20
Aspirin	54.5%	55.2%	0.51
Statin	62.5%	61.7%	0.46
Fibrate	5.7%	6.1%	0.40
Fasting serum glucose (mg/dl)	175.6 ±56.4	174.9 ±56.0	0.58
Glycated hemoglobin (%)	8.3 ±1.1	8.3 ±1.1	0.50
Serum creatinine (mg/dl)	0.91 ±0.23	0.91 ±0.24	0.20
Urine albumin/creatinine ratio (mg/g)	93.5 ±315.8	97.3 ±394.0	0.59
Potassium (mmol/L)	4.48 ±0.65	4.48 ±0.44	0.96
Total cholesterol (mg/dl)			
LDL cholesterol	105.0 ±33.9	105.0 ±33.9	0.97

Characteristic	Standard (N = 5042)	Intensive (N = 5040)	<i>P-value</i>
HDL cholesterol	42.0 ±1.5	41.9 ±11.8	0.65
Triglycerides	189.5 ±149.0	191.0 ±148.8	0.60

Table 2

Univariate predictors of cumulative probability of having new AF during follow-up presented as means with standard deviation or percent

Characteristic	Never had AF (N = 9,958)	Developed new AF (N = 159)	P-value
Age (years)	62.1 ±5.8	66.4 ±6.3	< 0.0001
Female sex	38.9%	27.7%	0.004
White	64.2%	84.9%	< 0.0001
Black	19.7%	6.9%	< 0.0001
Hispanics	19.7%	1.9%	< 0.0001
Weight (kgs)	93.3 ±16.5	100.4 ±20.1	< 0.0001
Waist (cm)	106.6 ±13.8	111.2 ±14.9	< 0.0001
Body mass index (kg/m ²)	32.2 ±5.5	33.4 ±5.5	0.007
Smoking	27.9%	25.8%	0.70
Duration of DM (years)	10.87 ±7.77	10.37 ±7.67	0.42
ECG LV hypertrophy	5.2%	4.4%	0.66
Systolic blood pressure (mmHg)	136.4 ±17.1	137.4 ±16.6	0.45
Diastolic blood pressure (mmHg)	74.9 ±10.6	71.0 ±10.1	< 0.0001
Pulse pressure (mmHg)	61.4 ±14.6	66.4 ±16.4	0.0002
Heart rate (bpm)	72.7 ±11.7	67.2 ±11.8	< 0.0001
Previous CV event	35.0%	41.5%	0.090
Previous heart failure	4.5%	10.1%	0.021
Medications			
Insulin	34.9%	34.0%	0.81
Metformin	60%	54.6%	0.38
Any sulfonylurea	50.0%	47.8%	0.55
Any antihypertensive agent	85.2%	93.7%	<0.0001
ACE-inhibitors	52.8%	58.5%	0.15
ARBs	16.0%	18.2%	0.44
Any thiazide diuretic	19.3%	18.2%	0.73
Beta-blockers	28.8%	42.1%	0.0002
Alpha-beta blockers	2.6%	3.8%	0.45
Dihydropyridine CCBs	11.6%	13.8%	0.39
Non-dihydropyridine CCBs	7.0%	10.7%	0.13
Aspirin	54.7%	62.2%	0.056
Statin	62.1%	63.5%	0.71
Fibrate	0.59%	8.2%	0.30
Fasting serum glucose (mg/dl)	175.2 ±56.3	175.4 ±48.8	0.96
Glycated hemoglobin (%)	8.30 ±1.05	8.31 ±0.95	0.92
Serum creatinine (mg/dl)	0.909 ±0.230	1.003 ±0.264	< 0.0001
Urine albumin/creatinine ratio (mg/g)	95.8 ±359.2	95.5 ±230.2	0.99
Potassium (mmol/L)	4.48 ±0.56	4.51 ±0.46	0.31
Total cholesterol (mg/dl)			

Characteristic	Never had AF (N = 9,958)	Developed new AF (N = 159)	P-value
LDL cholesterol	105.0 ±33.9	101.9 ±30.6	0.26
HDL cholesterol	41.9 ±11.7	41.6 ±9.8	0.68
Triglycerides	190.4 ±149.3	174.5 ±103.0	0.059

Table 3

Multivariate Predictors of new-onset AF in univariate and multivariate analysis.

Variable	Hazard Ratio	95% CI	P-value
Age (years)	1.065	(1.060-1.111)	< 0.0001
Weight (kilograms)	1.034	(1.025-1.043)	< 0.0001
Diastolic blood pressure (mmHg)	0.977	(0.961-0.994)	0.0065
Heart rate (bpm)	0.968	(0.954-0.983)	< 0.0001
Previous heart failure	1.912	(1.123-3.253)	0.017