Role of Diabetes and Insulin Use in the Risk of Stroke and Acute Myocardial Infarction in Patients with Atrial Fibrillation: a Medicare Analysis

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Abstract

Background: Atrial fibrillation (AF) is associated with elevated risk for ischemic stroke and myocardial infarction (MI). The aim of the study is to assess the role of insulin use on the risk of stroke and MI in AF patients with diabetes.

Methods: We identified Medicare beneficiaries with new AF in 2011-2013. Primary outcomes were ischemic stroke and MI. Multivariate Cox regression models were used to assess the association between AF and time to stroke and MI. We adjusted for anticoagulant as a time-dependent covariate.

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Results: Out of 798,592 AF patients, 53212 (6.7%) were insulin-requiring diabetics (IRD), 250214 (31.3%) were non-insulin requiring diabetics (NIRD) and 495166 (62%) were non-diabetics (ND). IRD had a higher risk of stroke when compared to NIRD (adjusted HR: 1.15, 95% CI 1.10-1.21) and ND (aHR 1.24, 95% CI 1.18-1.31) (P<0.01 for both). The risk of stroke was higher in NIRD compared to ND (aHR 1.08, 95% CI 1.05-1.12). For the outcome of MI, IRD had a higher risk compared to NIRD (aHR 1.24, 95% CI 1.18-1.31) and ND (aHR 1.46, 95% CI 1.38-1.54)]. NIRD had a higher risk compared to ND (aHR 1.17, 95% CI 1.13-1.22). Anticoagulation were most effective at preventing stroke in ND [0.72 (0.69-0.75)], and NIRD [0.88 (0.85-0.92)], but were not associated with significant reduction in stroke in IRD [0.96 (0.89-1.04)].

Conclusion: There is an incremental risk of ischemic stroke and MI from non-diabetics to non-insulin diabetics with the highest risk in insulin users. Protective effect of anticoagulation is attenuated with insulin use.

Keywords

Atrial fibrillation; Diabetes mellitus; Insulin therapy; anticoagulation; stroke; myocardial infarction

Introduction

Patients with non-valvular atrial fibrillation (AF) have 3 – 5 fold higher risk of stroke and acute myocardial infarction (Ml). [1–3] There are two predominant mechanisms that orchestrate these cardiovascular (CV) outcomes in patients with AF: 1) thromboembolism; embolization of left atrial clot to distant vascular beds leading to ischemia[4], 2) atherothrombosis; a state of systemic inflammation associated with AF that potentially accelerates atherosclerosis and creates a prothombotic state that leads to enhanced platelet activation and thrombosis. [5,6]

Diabetes mellitus (DM) significantly increases risk of CV events in patients with AF. As a result, DM was included in the most widely accepted risk scoring algorithms; the $CHADS_2$ and the CHA_2DS_2-VASc scores.[7,8] However, important knowledge gaps exist in our understanding of the mechanism via which DM increases risk of CV outcomes in patients with AF. One study showed that longer duration of DM, not poor glycemic control per se, increases stroke risk. [9] On the other hand, another study showed that insulin use, and not the presence of DM, is the factor that increases risk of stroke.[10] Given that DM is present in about 15% of AF patients, it is important to better define the role of insulin in risk of stroke and MI in AF diabetic patients. [11] Furthermore, it is unknown whether oral anticoagulation (OAC) therapy is equally effective in different DM types.

We used Medicare claims data to compare outcomes of stroke and MI in AF patients who were insulin-requiring diabetics (IRD), non-insulin requiring diabetics (NIRD) and non-diabetics. We also assessed the protective effect of OAC against both outcomes in presence of insulin use.

Methods

The institutional review board of the University of Iowa approved the study protocol. Considering the retrospective cohort design of this investigation the need for informed consent was waived. We used Centers for Medicare & Medicaid (CMS) data from November 2011 to October 2013, including: 1) beneficiary summary file base and chronic conditions segments; 2) inpatient (part A) and carrier (part B) standard analytic files; and 3) pharmacy drug event (part D). Patients were included in the study if they had AF diagnosis during the period November 2011 through October 2013. AF was defined based on previously published algorithms (i.e., 1 inpatient claim or 2 outpatient claims within a year with International Classification of Diseases-Ninth Revision-Clinical Modification [ICD-9-CM] code 427.31 as primary or first secondary diagnosis).[12,13] We excluded patients if they were younger than 66 years at the time of diagnosis (to ensure at least 12 months of Medicare eligibility before diagnosis), were enrolled in a Medicare managed care during the observation period, or were not enrolled in a Part D drug prescription plan at the time of AF diagnosis. Using these criteria we identified 828,051 patients with AF. From this, we excluded 29,459 patients whose AF diagnosis occurred during the same hospitalization as open-heart surgery or within 30 days, as these may represent post-operative AF. Hence, our final study cohort comprised of 798,592 patients with AF.

Exposure and cohort definition

DM diagnosis was identified using ICD-9-CM codes (250.xx). Study cohort participants were identified as IRD if they had a diagnosis of DM and were using insulin at the time of AF diagnosis. Insulin type (short vs. long acting) and dosage were identified in insulin users. Participants were defined as NIRD if they had a diagnosis of DM at the time of AF diagnosis but were not using insulin. Prevalence of different oral hypoglycemics use was identified and was classified into metformin, thiazolidiones, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas. Finally, non-diabetics were those study participants without a diagnosis of DM.

We identified patient characteristics from Medicare enrollment data and inpatient and carrier claims. Age, sex, and race were identified from Medicare enrollment data. Comorbid diseases defined by Elixhauser et al. were identified by ICD-9-CM diagnoses in inpatient and outpatient claims during the 12 months preceding AF diagnosis.[14] We identified additional comorbidities of importance to AF outcomes, including: other dysrhythmias (ICD-9-CM codes 427.X, excluding 427.3), cardiomyopathy (ICD9 codes 425.X), cardiac conduction disorder (e.g. bundle branch block; ICD9 codes 426.X), and previous implantable cardiac device (e.g. pacemaker; ICD9 codes V45.0, V53.3). To avoid multicollinearity, the CHA_2DS_2-VASc stroke risk score was calculated without the DM element of it (1 point each for congestive heart failure diagnosis, female sex, hypertension diagnosis, age 65-75 years, and vascular disease diagnosis; 2 points each for age >75 years and prior stroke or transient ischemic attack). [8] The HAS-BLED (Hypertension, Abnormal renal and liver functions, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol) score was used to represent bleeding risk in our study patients.[15] To adjust for diabetes duration as a risk factor, we used presence of microvascular diabetic complications as a proxy to duration

(defined with the following ICD-9 codes: 250.4× for renal complications, 250.5× for ophthalmic complications, and 250.6× for neurological complications and 250.7× for peripheral circulatory complications). Further we calculated health care utilization during the 12 months prior to AF diagnosis (number of inpatient hospital days, skilled nursing facility stay and extended care stay) and medication use within 90 days of AF diagnosis (insulin, statins, beta blockers, calcium channel blockers, aspirin, clopidogrel, proton pump inhibitors, amiodarone, non-steroidal anti-inflammatory drugs, and oral hypoglycemics). Use of oral anticoagulants after AF diagnosis was also assessed.

Study outcomes

Inpatient hospitalizations for incident stroke and incident MI were the outcomes assessed in this study. We followed the definition reported by Rothendler et al based on the primary ICD-9-CM diagnosis on inpatient standard analytical file claims for acute care stays to define incident stroke in our study [16,17]. Similarly, primary ICD-9-CM codes from inpatient claims were used to identify MI admissions. Patients were followed from the time of initial AF diagnosis until the outcome of interest (stroke or MI), death, or end of follow-up (December 31st 2013).

Statistical analysis

The study cohort was divided into IRD, NIRD and ND using criteria mentioned above. Continuous variables were reported as mean (standard deviation) or median (interquartile range) depending on the normality of data distribution. Categorical variables were reported as number and percentages. We used chi-square test or 1-way analysis of variance, as appropriate, to compare demographic variables, comorbid conditions, health care utilization, medication use, CHA_2DS_2-VASc and HAS-BLED scores between the 3 groups. Then we reported the study outcomes, stroke and MI, as number of events, percentage and events/ hundred patient years of follow-up separately for the 3 groups. We used Cox proportional hazards regression, with time to stroke and time to MI as dependent variables and the 3 diabetes categories as independent variables, to assess the hazard of the respective outcomes comparing the 3 DM categories to each other. Additional models were estimated using Fine & Gray's [18] approach to competing events to account for censoring due to death; results were nearly identical to those reported. Nearly 50 variables that may confound the association between DM and the study outcomes were candidates for multivariable models (Supplemental Table 1). Candidate variables were assessed for multicollinearity, and variables were selected for inclusion in Cox models based on relationship to the outcome (using a statistical criterion of 0.05), and consistency with prior literature and clinical experience. We repeated the Cox regression models after including anticoagulant use as a time dependent variable, in order to assess the relative effect of anticoagulation by diabetes category. We assessed the impact of the interaction between diabetes type and anticoagulation on the outcomes stroke and MI using a multiplicative model and also using an additive model (i.e. relative excess risk due to interdependence (RERI) as described by VanderWeele and Knol.[19] The results of the Cox models were reported as hazard ratios (HR) and 95% confidence intervals. Analysis was done with SAS version 9.4 (SAS Institute, Cary, North Carolina) and R 3.4.3 (R foundation for Statistical Computing, Vienna, Austria). P value < 0.05 was considered statistically significant. This study is supported by funding

from the Agency for Healthcare Research and Quality and by the health services research and development service of the department of Veterans Affairs. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

A total of 798,592 patients with AF formed the final study cohort. Among them, 53,212 (6.7%) were IRD, 250,214 (31.3%) were NIRD and 495,166 (62%) were ND. Table 1 details the demographic variables, comorbid conditions, risk scores, health care utilization and medication use comparisons between the 3 DM categories. In particular, IRD were younger, less likely to be women and more likely to be African American compared to the other DM categories. Further, IRD had a significantly greater proportion of comorbid diseases compared to the other 2 DM categories. Mean CHA_2DS_2-VASC score, FIAS-BLED score, and Gagne score were higher in the IRD compared to the other 2 DM groups. Also, health care utilization and cardiac medication use were also higher in the IRD compared to the other 2 groups. Oral anticoagulation use was highest in IRD, with warfarin the most used anticoagulant during our study period. Table 1 shows comparative persistence of OAC use among the three groups.

Table 2 details the event rates of stroke and MI. Unadjusted rates of stroke and MI were highest in IRD patients, followed by the NIRD. The ND had the lowest unadjusted event rate. Table 3 details the hazard of stroke and MI comparing the 3 DM groups. In the adjusted model, IRD had higher risk of stroke compared to NIRD (Hazards ratio (HR): 1.15 (95% confidence interval (CI) 1.10 – 1.21)] and ND [HR 1.24 (95% CI 1.18 – 1.31), p<0.001 for both], NIRD had higher risk of stroke compared to ND [HR 1.08 (95% CI 1.05 – 1.12), p<0.001]. Supplemental Table 2 shows the full-adjusted model for the outcome of stroke. When anticoagulant use was added to the model as a time dependent variable, the overall hazard ratio (HR) for stroke associated with anticoagulant use was 0.85 (95% CI, 0.83 - 0.87; p<0.001). However, there was a significant interaction between diabetes category and anticoagulant use (p<0.001). Anticoagulants were most effective at preventing stroke in ND (HR=0.74; 95% CI, 0.72-0.77; p<0.001), and NIRD (HR=0.86; 95% CI, 0.83-0.90; p<0.001), but were not associated with significant reduction in stroke among patients using insulin (HR=0.94 (0.87-1.02; p=0.09). Similarly in the relative excess risk due to interdependence (RERI) model, anticoagulation use was not associated with significant reduction in stroke risk among IRD patients (RERI=0.0001, 95% CI (–0.1559, 0.1562), p=NS). When analysis was restricted to patients who never initiated OAC, and in analysis that separately examined patients with and without any OAC in the first 365 days after AF diagnosis, results remained the same (Table 3).

For the outcome of MI, in the adjusted model, IRD had a higher risk of MI compared to NIRD [HR 1.24 (95% CI 1.18 – 1.31)] and ND [HR 1.46 (95% CI 1.38 – 1.54), P<0.001 for both]. Similarly, NIRD had higher risk of MI compared to ND [1.17 (1.13 – 1.22), p<0.001]. Supplemental Table 3 shows the full-adjusted model for the outcome of MI. When anticoagulant use was added to the model as a time dependent variable, the overall hazard ratio (HR) for MI associated with anticoagulant use was 0.86 (95% CI, 0.83-0.88; p<0.001).

Similar to stroke, there was a significant interaction between diabetes category and anticoagulant use (p<0.001). Anticoagulants were most effective at preventing MI in ND (HR=0.84; 95% CI, 0.81-0.87; p<0.001), and NIRD (HR=0.85; 95% CI, 0.82-0.90; p<0.001), but were not associated with significant reduction in MI among patients using insulin (HR=0.94; 95% CI, 0.86-1.02). Similarly on the additive model with relative excess risk due to interdependence model, anticoagulation was not associated with significant reduction in MI risk in IRD (RERI=0.0099, 95% CI (–0.1297, 0.1494), P=NS).

Discussion

We report several findings in this study of Medicare population with AF. First, there was a significant incremental risk for stroke and MI in our three groups based on diabetic status and insulin use, where IRD had the highest risk, followed by NIRD and then non-diabetics. Second, while OAC therapy was effective overall in reducing risk of stroke and MI, this protective effect was diminished in diabetic AF patients who used insulin.

Multiple mechanisms may explain the hierarchical risk association, whereby IRD have the highest risk for both stroke and MI outcomes, followed by NIRD and then ND. First, DM can alter the left atrium both structurally (deposition of glycated products and connexin-mediated fibrosis) and electrically (affecting intra-atrial conduction)[20,21], thereby promoting thromboembolism. Second, DM, in addition to accelerating atherosclerosis, is associated with higher levels of Von Willibrand factor, soluble P-selectin, and markers of platelet activation and inflammation [22,23]. These mechanisms increase risk of atherothrombosis. Finally, IRD, by virtue of having more advanced disease and/or via exogenous insulin use, are hypercoagulable [24] with a higher tendency to form clots [25–27] and have greater oxidative stress and inflammation. [28,29]

Our study raises the question whether advanced diabetes requiring insulin therapy confers a significantly elevated risk of thromboembolism beyond what can be mitigated by anticoagulant therapy, and whether this should be reflected in scores used to calculate risk for stroke and MI in AF patients (e.g., CHA_2DS_2-Vasc). In a recent study from the prospective PREFER registry,[10] stroke risk was higher in IRD, compared to NIRD and ND. However, contrary to our study, risk of stroke was similar between NIRD and ND. This could be due to the small sample size of NRD included in that study (n=1000) compared to 250,000 in our study, given that the magnitude of risk difference is modest in our study. Furthermore, in the PREFER study, controlling for OAC use did not alter their findings. Other studies using contemporary AF registries such as the ORBIT-AF and others have shown that among anticoagulated patients with AF, the risk of stroke in all DM patients were similar to their counterparts without DM [30,31] . They attribute this attenuation of risk in DM patients to effective anticoagulation. These studies did not examine stroke risk according to insulin use among DM patients, and failure to distinguish IRD and NIRD may dilute any increased stroke risk among DM patients. However, comparative inference that may be drawn based on these registries, our analysis, and Patti et el. [10], is that anticoagulation may mitigate thromboembolic risk in most diabetic patients except those with advanced disease who have the need for insulin to maintain euglycemia.

Similar to our findings regarding stroke risk, the risk of MI (an atherothrombotic outcome) also suggests a hierarchical risk association: IRD had highest risk, followed by NIRD and then ND. We were unable to find another study that had assessed MI outcome by categories of insulin use among DM patients with AF. In a sub-study by Marzona et al [32] that included patients with DM at very high risk and one or more CV risk factors or microvascular disease, multivariate analysis showed that insulin treatment in diabetics was associated with 81% risk of major CV events (non-fatal MI, non-fatal stroke and CV death) compared with no insulin treatment. That study was however not limited to patients with atrial fibrillation and there was no comparison to non-diabetics. In a study using the ORBIT-AF [30] registry, DM patients had higher risk of CV hospitalization, sudden cardiac death and CV mortality compared to patients without DM in spite of anticoagulation use. As with stroke, MI outcomes were not reported by categories of insulin use. From ORBIT-AF and our results, it may be inferred that anticoagulation alone may not suffice to decrease risk of CV outcomes in AF patients with advanced DM requiring insulin. A question remains whether direct oral anticoagulants such as dabigatran or apixaban offer better protection in this setting or not.

An analysis using Framingham data[33] showed that although DM significantly increased risk of cardiovascular events, much of this excess risk may be attributed to comorbid diseases like hypertension and advanced renal impairment (nearly 30 - 40% attributable risk). Hence, it may be the comorbid illnesses that accompany DM, rather than DM itself, that increases MI risk and also explains the increased MI risk in all DM patients regardless of insulin use. It is unclear whether exogenous insulin use increases adverse outcomes in IRD, or whether insulin use represents advanced disease that predisposes patients with DM to worse outcomes. Explaining these important pathological underpinnings is beyond the scope of our paper and future studies are needed to answer these questions. It may be of interest to see if newer oral hypoglycemic drugs such as glucagon-like peptides or sodium glucose cotransporter-2 inhibitors can be used in lieu of insulin in high risk patients to further reduce adverse outcomes [34].

Although the strengths of our study include using a large, nationally representative sample, with robust adjustment for confounders, several limitations of our analysis needs to be considered. First, we lacked some prognostic variables that may be related to stroke risk, such as duration of diabetes, insulin dose, and glycated hemoglobin values. However, we used presence of microvascular complications as a proxy measure to duration of diabetes in our models. Second, for the outcome of MI, patients hospitalized for AF may have had troponin elevation because of the mechanism of demand-supply mismatch and could have received a diagnosis of MI. This is a known limitation of ICD-9 based MI outcome determination [35]. Future prospective studies with validated MI outcome determination are needed. Also, we had a relatively short follow-up period after AF diagnosis (median 14 months). Hence it needs to be determined if these associations will persist with longer follow-up. We also lacked information on INR levels in patients who were using warfarin and time in therapeutic range. Finally, we did not control for possible differences in anticoagulation adherence in our analysis, which may explain the lack of effective stroke and MI protection in IRD patients if IRD patients have poorer adherence or persistence compared to NIRD and ND patients. However, additional analysis revealed that OAC

persistence is at least as good or better among IRD patients compared to the other two groups (e.g., among patients who initiated OAC, the prevalence of at least three months of continuous use of OAC in insulin-requiring diabetics was 45.3% compared to 41.9% and 41.8% in non-insulin diabetics and nondiabetics, respectively (p<0.001). Given that persistence of OAC use in insulin-requiring diabetics was at least as good or better than OAC use in non-insulin diabetics and non-diabetics, differences in OAC persistence do not explain the poor efficacy of OAC use in insulin-requiring diabetics.

In conclusion, among patients with AF, IRD is associated with higher risk of thromboembolic and atherothrombotic outcomes compared to NIRD and ND. In fact IRD appear to derive the least benefit from anticoagulation in terms of mitigating these risks. Hence, future studies should assess if incorporation of IRD in stroke prediction risk algorithms will improve stroke prediction in this high risk group and whether DOAC's or new diabetic medications might offer additional protection against CV outcomes in this setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- Risk of stroke and MI is incremental in AF diabetic patients.

- Risk of stroke in AF is higher in insulin versus non-insulin requiring diabetics.

- Risk of MI in AF is higher in insulin versus non-insulin requiring diabetics.

- Insulin use seems to attenuate the protective effect of oral anticoagulation in AF.
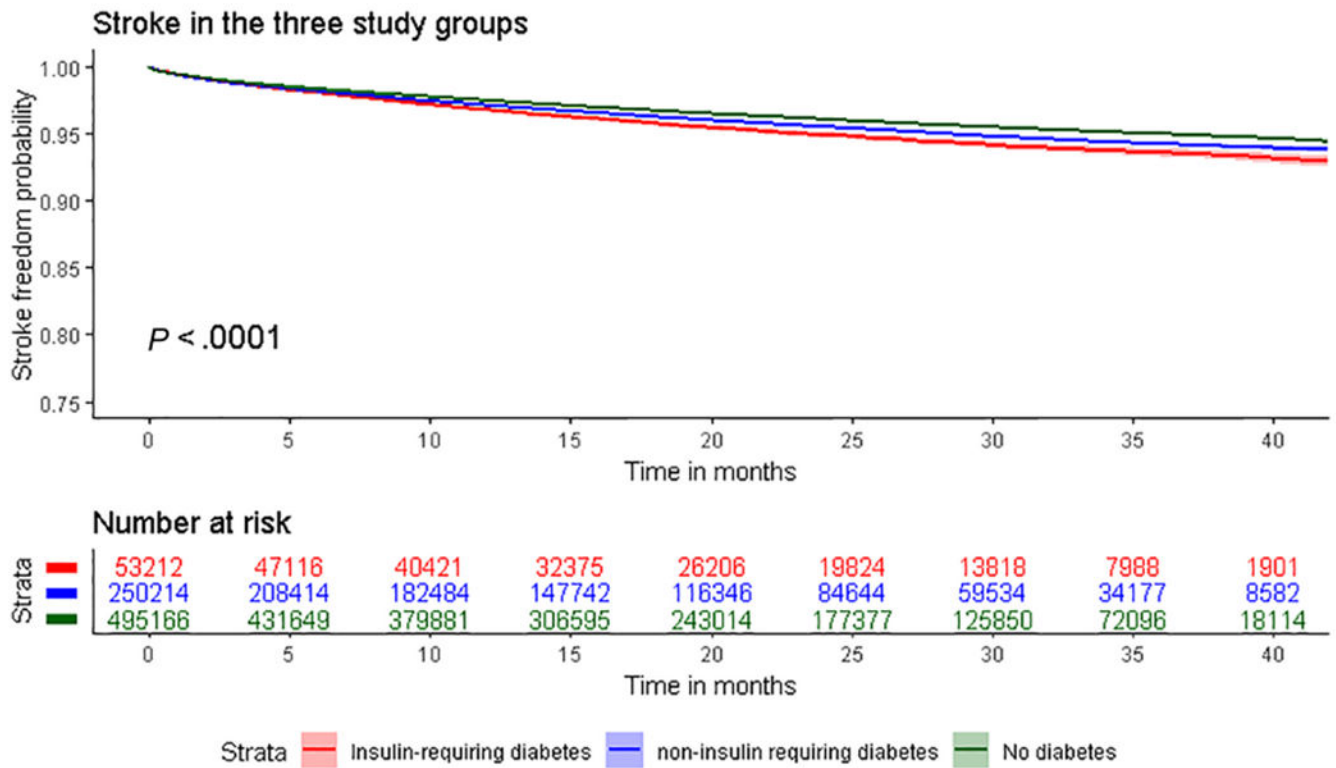
Figure 1:
Kaplan Meier curves for the outcome stroke in the three study groups. Log-rank test p
<0.0001
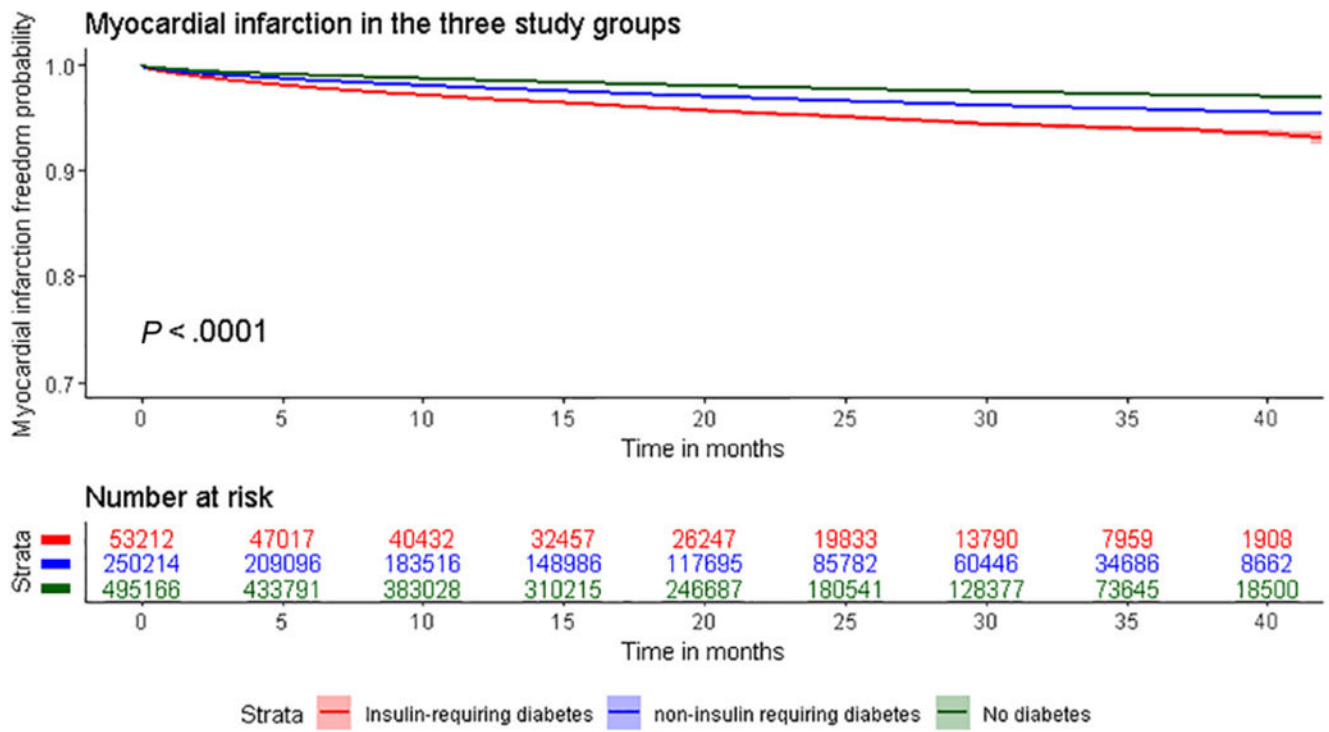
Figure 2:
Kaplan Meier curves for the outcome acute myocardial infarction in the three study groups.
Log-rank test p <0.0001

Table 1:

Baseline characteristics of the study three groups

Variables	Insulin requiring diabetics	Non-insulin requiring diabetics	Non-diabetics	P value
	(N =53,212)	(N = 250,214)	(N = 495,166)	
Age				
Mean age (years)	77.1	78.5	79.7	<0.001
65 – 74 years – n (%)	22,374 (42.1)	86,707 (34.7)	153,291 (30.9)	<0.001
75 – 84 years – n (%)	20,962 (39.4)	102,141 (40.8)	187,894 (37.9)	
> 85 years – n (%)	9,876 (18.6)	61,366 (24.5)	153,981 (31.1)	
Women – n (%)	30,866 (58.0)	139,829 (55.9)	297,336 (60.0)	
Race				
White – n (%)	39,755 (74.7)	196,782 (78.7)	439,855 (88.8)	<0.001
Black – n (%)	6,083 (11.4)	24,149 (9.7)	24,624 (4.9)	
Asian – n (%)	1,621 (3.1)	8,064 (3.2)	9,609 (1.9)	
Hispanics – n (%)	5,111 (9.6)	18,520 (7.4)	17,472 (3.5)	
Native – n (%)	239 (0.5)	968 (0.4)	1,328 (0.3)	
Others – n (%)	403 (0.8)	1,731 (0.7)	2,278 (0.5)	
Comorbid diseases				
Hypertension- n (%)	50,567 (94.8)	236,279 (94.4)	406,378 (82.1)	<0.001
Heart failure– n (%)	29,921 (56.2)	112,585 (45.0)	151,274 (30.6)	<0.001
Prior stroke – n (%)	8,931 (16.8)	38,913 (15.6)	60,533 (12.2)	<0.001
Prior transient ischemic attack – n (%)	4,259 (8.0)	20,014 (8.0)	32,654 (6.6)	<0.001
Prior Myocardial infarction– n (%)	12,131 (22.8)	46,991 (18.7)	61,889 (12.5)	<0.001
Peripheral vascular disease – n (%)	21,976 (41.3)	89,111 (35.6)	127,151 (25.7)	<0.001
Diabetes complications – n (%)	34,419 (64.7)	93,646 (37.4)	0	<0.001
Obesity – n (%)	14,430 (27.1)	45,426 (18.2)	35,722 (7.2)	<0.001
Prior valvular heart disease – n (%)	18,450 (34.7)	89,349 (35.7)	155,186 (31.3)	<0.001
Prior cardiomyopathy – n (%)	8,050 (14.5)	32,095 (12.3)	42,313 (8.3)	<0.001
Prior conduction disorders – n (%)	8,878 (16.7)	38,585 (15.4)	59,433 (12.0)	<0.001
Other arrhythmias – n (%)	22,419 (42.1)	106,554 (42.6)	188,615 (38.1)	<0.001
Renal disease – n (%)	24,922 (46.8)	84,979 (32.4)	86,525 (17.5)	<0.001
Liver disease – n (%)	4,447 (8.4)	20,575 (8.2)	24,517 (4.9)	<0.001
Prior coagulation disorders – n (%)	65,00 (12.2)	29,838 (11.9)	41,004 (8.3)	<0.001
Prior alcohol use – n (%)	638 (1.2)	3,381 (1.4)	6,455 (1.3)	0.014
Prior peptic ulcer disease – n (%)	1,645 (3.1)	8,054 (3.2)	11,546 (2.3)	<0.001
Prior depression – n (%)	13,826 (25.9)	50,292 (20.1)	81,282 (16.4)	<0.001
Prior dementia – n (%)	7,812 (14.7)	27,688 (11.7)	46,645 (9.4)	<0.001
Prior bleeding – n (%)	1,245 (2.3)	5,881 (2.4)	8,993 (1.8)	<0.001
Comorbidity scores				

Variables	Insulin requiring diabetics	Non-insulin requiring diabetics	Non-diabetics	P value
Mean CHA$_2$DS$_2$VASC score [*]	5.2	5.0	4.5	<0.001
HAS-BLED score	3.4	3.2	2.7	<0.001
Health care utilization				
Number of inpatient hospital days	11.6	9.9	6.1	<0.001
Skilled nursing facility stay – n (%)	13,468 (24.3)	39,554 (15.2)	53,615 (10.5)	<0.001
Extended care stay – n (%)	17,302 (31.2)	52,224 (20.0)	76,960 (15.1)	<0.001
Medication use at time of AF diagnosis				
Statin use – n (%)	31,099 (58.4)	120,060 (47.9)	174,430 (35.2)	<0.001
Beta-blockers – n (%)	29,150 (54.8)	114,678 (45.8)	195,215 (39.4)	<0.001
Calcium channel blockers – n (%)	5,580 (10.5)	22,836 (9.1)	45,347 (9.2)	<0.001
Clopidogrel – n (%)	5,643 (10.6)	20,075 (8.0)	26,644 (5.4)	<0.001
Proton pump inhibitors – n (%)	24,218 (45.5)	89,092 (35.6)	144,752 (29.2)	<0.001
NSAIDS – n (%)	13,742 (25.8)	61,385 (24.5)	104,650 (21.1)	<0.001
Insulin Glargine	23853 (44.8)	0	0	NA
Insulin Detemir	5574 (10.5)	0	0	NA
Insulin Aspart	8909 (16.7)	0	0	NA
Insulin Lispro	4966 (9.3)	0	0	NA
Regular insulin	5692 (10.7)	0	0	NA
Metformin	7567 (14.2)	37056 (14.8)	2388 (0.5)	<0.001
Thiazolidiones	1117 (2.1)	5223 (2.1)	0	<0.001
DPP-4 inhibitors	2983 (5.6)	9020 (3.6)	0	<0.001
Sulfonylureas	8354 (15.7)	33947 (13.6)	0	<0.001
Any Oral anticoagulation	30,561 (57.4%)	131,890 (52.7%)	260,020 (52.5%)	<0.001
Warfarin	24,914 (46.8%)	98,952 (39.6%)	190,959 (38.6%)	<0.001
Dabigatran	3965 (7.5%)	22,323 (8.9%)	48,331 (9.8%)	<0.001
Rivaroxaban	3271 (6.2%)	18,231 (7.3%)	40,286 (8.1%)	<0.001
Total duration of warfarin use Median (IQR), days	367 (114-745)	349 (110-742)	365 (114-776)	<0.01 [**]
Total duration of any anticoagulation Median (IQR), days	371 (127-735)	355 (133-725)	365 (138-746)	<0.01 [***]
At least 3 months of anticoagulation	45.3%	41.9%	41.8%	<0.01

[*] CHA$_2$DS$_2$-Vasc score was calculated without points for diabetes

[**] P=0.005 for comparison between insulin and non-insulin requiring diabetics, and P=0.04 for comparison between insulin diabetics and non-diabetics.

[***] P=0.04 for comparison between insulin and non-insulin requiring diabetics, P=0.17 for comparison between insulin requiring and nondiabetics.

Table 2:

Primary study outcomes, stroke and acute myocardial infarction (MI), in the three study groups

		Insulin requiring diabetics	Non-insulin requiring diabetics	Non-diabetics	P value
Stroke	Number of events	2,347 (4.4%)	9,314 (3.7%)	16,797 (3.4%)	<0.001
	Event rate per 100 person-year follow up	2.6	2.3	2.0	
MI	Number of events	2,274 (4.3%)	7,014 (2.8%)	9,632 (1.9%)	<0.001
	Event rate per 100 person-year follow up	2.5	1.7	1.1	

Table 3:

Relative hazard of Stroke and Myocardial Infarction by diabetes group based on multivariable Cox regression models with and without controlling for oral anticoagulant use

Outcome	Model	Hazard ratio	95% confidence interval	P value
Stroke	**Without adjusting for anticoagulation**[*]			
	Insulin requiring diabetics vs. non-diabetics	1.24	1.18-1.31	<0.01
	Insulin vs. non-insulin requiring diabetics	1.15	1.10-1.21	<0.01
	Non-insulin requiring diabetics vs. non-diabetics	1.08	1.05-1.12	<0.01
	With time dependent anticoagulation use[*]			
	Insulin requiring diabetics vs. non-diabetics	1.24	1.18-1.31	<0.01
	Insulin vs. non-insulin requiring diabetics	1.15	1.09-1.20	<0.01
	Non-insulin requiring diabetics vs. non-diabetics	1.08	1.05-1.12	<0.01
	In patients who did not use anticoagulation[*]			
	Insulin-requiring diabetics vs. non-diabetics.	1.21	1.11-1.32	<0.01
	Non-insulin requiring diabetics vs. non-diabetics	1.08	1.03-1.14	0.002
	Insulin vs. Non-insulin requiring diabetics	1.12	1.04-1.21	0.005
MI	**Without adjusting for anticoagulation**[*]			
	Insulin requiring diabetics vs. non-diabetics	1.46	1.38-1.54	<0.01
	Insulin vs. non-insulin requiring diabetics	1.24	1.18-1.31	<0.01
	Non-insulin requiring diabetics vs. non-diabetics	1.17	1.13-1.22	<0.01
	With time dependent anticoagulation use[*]			
	Insulin requiring diabetics vs. non-diabetics	1.47	1.39-1.55	<0.01
	Insulin vs. non-insulin requiring diabetics	1.25	1.19-1.31	<0.01
	Non-insulin requiring diabetics vs. non-diabetics	1.18	1.13-1.22	<0.01

[*] Cox multivariable models controlled for patient demographics (age, sex, race), comorbidity, diabetes microvascular complications, medication use at time of AF diagnosis, and prior health services use. Full models are shown in supplemental material.