HHS Public Access

Author manuscript

Am J Cardiol. Author manuscript; available in PMC 2021 September 15.

Published in final edited form as:

Am J Cardiol. 2020 September 15; 131: 33–39. doi:10.1016/j.amjcard.2020.06.049.

Impact of Diabetes Mellitus on Stroke and Survival in Patients with Atrial Fibrillation

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Abstract

Although diabetes mellitus (DM) has been established as a risk factor for developing atrial fibrillation (AF) and is a known risk factor for stroke, it is unclear whether the presence or duration of DM is the primary adverse influence on the clinical course of AF. We retrospectively analyzed patients diagnosed with incident AF to examine the impact of DM on ischemic stroke and all-cause mortality. The diagnosis of DM was established by ICD-9 codes and review of medical records. To account for the significant differences in baseline characteristics of patients with and without diabetes, we matched 909 AF patients with DM with 909 AF patients without DM using propensity score matching based on 26 baseline variables. Cox regression analysis was used to identify independent factors associated with ischemic stroke and mortality. The mean age of the propensity matched cohort was 74 ± 11.5 years and 55.4% were male. Over a median follow-up period of 5.4 years (maximum 23.9 years), cumulative survival was significantly lower for patients with DM than those without DM; Log-rank P<.001. In the propensity-matched comparison, the risk of mortality was significantly higher in the DM group compared with the

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DISCLOSURES

All authors have not reported any relationships relevant to the contents of this paper to disclose.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

non-DM group [Hazard ratio (HR) 1.25; 95% confidence interval (CI) 1.12–1.69; P<.001]. Likewise, patients with DM had a higher risk of stroke (HR 1.32; 95% CI 1.02–1.69; P=0.03). Duration of DM was not associated with increased risk for stroke or mortality. In conclusion, the comorbidity of DM represents an independent predictor of reduced survival and further highlights the excess risk of thromboembolism in patients with AF.

Keywords

Atrial fibrillation; diabetes mellitus; survival; ischemic stroke

INTRODUCTION

Diabetes mellitus (DM) is a recognized risk factor for cardiovascular (CV) diseases and is strongly associated with atrial fibrillation (AF).[1–4] The association between DM and AF is likely multifactorial, but oxidative stress and pro-inflammatory changes and consequent atrial remodeling have been suggested to initiate and maintain AF in diabetic patients.[5,6] Contemporary evidence has shown that the co-existence of DM may complicate the clinical course and outcome of patients with AF,[7,8] along with substantially increased risks of ischemic stroke.[9–11] More recently, the duration of diabetes has also been advocated as a significant predictor of stroke risk in AF patients.[9,12] However, to date, the prognostic impact of concomitant DM and AF on survival, whether complimentary or supplementary, remain mostly unknown. While patients with both DM and AF have higher mortality compared to those with DM alone,[13] it remains unclear whether the presence of both conditions is uniquely associated with an elevated risk of mortality compared to those with AF alone without DM. Prior studies evaluating this question were limited by short follow-up duration, lack of information on important clinical variables such as the cause of death, duration of DM, glycemic control, and their influence on survival of patients with both DM and AF.[7,10] Therefore, using a community-based cohort of patients with incident AF, we investigated the impact of comorbid DM on the risks of mortality and ischemic stroke.

METHODS

The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards and waived the requirement for informed consent. This observational, retrospective cohort study was conducted in Olmsted County, Minnesota, which has an estimated 2010 population of 144,248 residents, 85.7% of whom are Caucasian. Extensive details about the Olmsted County population have been reported elsewhere.[14] Briefly, the population-based resources of the Rochester Epidemiology Project link and provide access to the medical records of all Olmsted County residents from all Olmsted County medical care providers, ensuring complete ascertainment of most medical conditions. We identified all Olmsted County residents who were diagnosed with or documented to have AF for the first time from 1980 to 2010. All AF events were verified as the first documented AF episode and confirmed by a 12-lead electrocardiogram, event monitor, Holter monitor, or cardiac implantable electronic devices. Patients with atrial flutter alone, without any evidence of AF, were not included in the study population. Patients with post-operative or

post-procedure AF that did not recur within 30 days after the index operation or procedure were also not included. DM was initially identified by ICD-9-CM codes from the underlying AF population and ascertained by review of the medical records. In general, patients were considered to have DM if they had a documented history of DM prior to AF diagnosis or were being treated with insulin or oral hypoglycemic medications or had qualifying laboratory glucose values consistent with DM[15]. The date these individuals first met the criteria was defined as the date they reported having been first assigned a diagnosis of DM.

The primary outcome of interest was all-cause mortality. The secondary outcome was ischemic stroke, which was defined as an episode of focal neurological dysfunction diagnosed as an ischemic stroke or transient ischemic attack by neuroimaging assessment or clinical diagnosis. Patients were followed from their AF diagnosis until December 31, 2017 for deaths. Mortality and cause of death were ascertained by post-mortem review of the medical records, death certificates, autopsy reports, obituary notices, and query of the Social Security Death Index using the patient's social security number. The cause of death was classified as cardiovascular or non-cardiovascular. Cardiovascular was defined as death due to ischemic heart disease, cardiomyopathy, cardiac arrest, stroke, or arrhythmias.

Categorical variables were expressed as numbers and percentages and compared with Pearson chi square or Fisher exact tests as appropriate. Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range [IQR]) for non-normally distributed data and were compared with a 2-sided unpaired Student t test or Wilcoxon rank sum test, as appropriate. The risk of death and ischemic stroke associated with diabetes was estimated by means of time-dependent Cox proportional-hazards models. The covariates included in the multivariable models were selected based on statistical evidence of a univariate association or known association with DM and these outcomes. Variables with complete or ≥80% complete data were entered stepwise into a multivariate Cox proportional hazards model to assess independent predictive value. Deaths were compared between AF patients with and without preexisting DM, as defined in the original cohort. The associated risk for each outcome was expressed as Hazard ratio (HR) with corresponding 95% confidence interval (CI). The event-free survival curve was plotted via the Kaplan-Meier method, with the statistical significance determined by the log-rank test. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). All p values were based on 2-sided tests and were considered statistically significant at $p < 0.05$.

Given that group assignment was nonrandom, confounding and selection biases were accounted for through a propensity score matching technique based on 26 baseline characteristics (Figure 1). Propensity score matching analysis was used to predict the probability of having a diagnosis of DM. We used propensity scores to balance baseline characteristics between DM and non-DM groups, reducing potential selection bias. Logistic regression models were iteratively assessed to determine the balance of baseline covariate proportions between study groups in the matched samples. The best and final model was the one that balanced covariates between study groups, as determined by standardized differences <0.10. After calculation of propensity scores, a greedy matching algorithm was used to identify one DM patient for each non-DM patient in the respective matched samples.

RESULTS

The initial study cohort included 6077 patients with AF among which 1832 (30.1%) had preexisting DM. From this initial cohort, we identified a propensity score matched cohort of 1818 patients (909 with DM and 909 without DM). The two groups were matched based on 26 baseline variables following which, the two groups were balanced in terms of age, sex and comorbidities as shown in Figure 1. The mean age of the propensity matched cohort was 74 (± 11.5) years; 55.4 % were male and the mean CHA_2DS_2-VASc score was 4.7 (±2.1). Baseline characteristics of the matched cohort are shown in Table 1.

In the matched cohort, during a median follow up period of 5.4 years (IQR 1.4–9.6), a total of 1373 (75.5%) patients died from all causes. Figure 2 illustrates the cumulative survival for the propensity score-matched groups over a maximum follow-up of 24 years. Overall, cumulative survival was significantly lower for the DM than Non-DM cohort, Log-rank P<.001. The 5-year patient survival rate in the DM group was 49.3% and 55.2% in the non-DM group (Log-rank P<.001). The risk of mortality was significantly higher in the DM group than the non-DM group, (HR 1.25; 95% CI, 1.12–1.39; P<.001). Other variables associated with increased risk of mortality were hypertension, coronary artery disease, previous history of heart failure, prior episodes of stroke or TIA, smoking, chronic lung disease, chronic kidney disease, and higher CHA_2DS_2-VASc score. Higher HbA_{1C} levels were also associated with increased risk of mortality (HR 1.07; 95% CI 1.04–1.10; P<.001) while duration of diabetes did not have any association in the DM group (P=0.32). In addition, utilization of rate control agents such as beta-blockers and calcium channel blockers, and antiarrhythmics was protective against all-cause mortality in the propensity matched cohort (Table 2). We also evaluated causes of death in these patients. There were no differences in the proportion of cardiovascular (30.5% vs 29.5%) and non-cardiovascular (46.5% vs 44.0%) deaths between the DM and the non-DM group. Congestive heart failure (14%) was the most common cause of death followed by malignancy (12%), myocardial infarction (12%), and sudden cardiac death (9%).

Among the 1818 patients in the propensity score matched cohort, 243 (13.4%) developed stroke during follow-up. The overall annualized stroke rate was 2.3% and increased progressively according to CHA_2DS_2-VASc score. The annual risks of ischemic stroke for CHA_2DS_2-VASc score 0 or 1 was <1%, 1.9% for score 2 and 7.9% for score 9. Compared with the non-DM group, the DM cohort had a significantly higher risk of stroke (HR 1.32; 95% CI, 1.02–1.69; *P*=0.03) (Figure 3). Older age, female sex, hypertension, prior history of stroke and higher CHA_2DS_2-VASc score were all associated with increased risk of stroke in these patients (Table 3). Duration of diabetes was not associated with the risk of stroke (P= 0.52).

DISCUSSION

In this propensity matched analysis with 24 years of follow up, we examined the impact of DM on long-term survival of patients with incident AF. Overall, the prevalence of DM in our cohort was 30%. DM was significantly associated with reduced survival of patients with AF even after accounting for other comorbidities. Overall, preexisting DM conferred a 25%

increased risk of all-cause mortality. We also found that patients with both DM and AF had significantly higher risk of stroke compared to patients with AF without DM. The presence of DM in patients with AF was associated with a 32% increased risk of stroke. Duration of DM did not have any association with all-cause mortality or the risk of stroke. The use of beta-blockers, calcium channel blockers and antiarrhythmics was associated with lower all-cause mortality, suggesting that the management of comorbidities could play a role in reducing excess mortality in patients with AF.

Our findings are consistent with previous studies, which also showed that DM among patients with AF is associated with an increased risk of all-cause mortality.[7,10] In a post-hoc analysis of the ORBIT-AF registry, diabetic patients had higher risk of mortality compared with those without DM. In contrast to our population-based study, data on the causes of death in that study were not available.[7] Analysis of the causes of death in our study showed no significant difference in the hazard of CV mortality between those with and without DM, suggesting that individual CV risk factors may affect AF patients similarly irrespective of associated DM. Moreover, the broad adherence to guideline-directed medical therapy to control CV risk factors in the modern era could also attenuate the impact of DM on CVD risk. Indeed, a recent study by Raghavan et al. showed that DM-related mortality was attenuated by cardiovascular risk factor control.[16]

The impact of glycemic control and DM duration on survival in patients with AF has not been fully investigated. In our study, we found that higher HbA_{1c} values were associated with an increased risk of mortality. This finding is consistent with earlier studies showing that poor glycemic control is associated with persistence and recurrence of AF, potentially affecting survival.[16,17] The effect of DM on cardiac electrophysiology affecting structural remodeling along with the metabolic changes have been implicated in increasing the CV risk in these patients.[18,19] It has also been suggested that the masking effect of DM on symptom presentation in patients with AF may delay timely identification and treatment of AF, thereby resulting in poor outcome.[20] Conversely, improved glycemic control appears to favorably influence outcomes in patient with DM.[21] We found that the use of oral hypoglycemic agents reduced the risk of mortality possibly due to better AF outcomes with the use of these drugs.[21–23]

Although several contemporary studies have shown no difference in the risk of thromboembolic events in AF patients with and without DM,[247] several others have consistently reported DM as a risk factor for ischemic stroke in patients with AF.[9,12,25] Although the annualized stroke rates generally increases with higher CHA_2DS_2-VASc score, the rates observed in our cohort were slightly lower than those observed by Lip GY et al. using the Birmingham 2009 schema.[11] The difference is likely due to the use of anticoagulation in our group (53%). More recently, two large studies evaluating the influence of DM and glycemic control in AF patients reported an increased risk of thromboembolic events in AF patients with longer duration of DM.[9,12] Additionally, older studies, along with a more recent study from Danish registries, reported a higher thromboembolic risk with increasing levels of HbA1c.[26–29] In contrast, despite the confirmed association between DM and stroke in our cohort, neither the duration of DM nor HbA1c levels had any impact on risk of stroke in the matched cohort. The ATRIA study

likewise found no association of glycemic control measured by HbA1c with the risk of stroke in patients with AF.[12] Taken together, our results suggest that improvement in DM care in the United States,[16] are reflected in improvements in DM-related mortality, supported by the attenuation of the association between DM and mortality after accounting for risk factor levels and treatment. The present study showed that DM has an essential impact on survival and stroke risk. Therefore, improved treatment of DM and CV risk control may play a key role in reducing DM-associated morbidity and mortality in patients with AF.

The major strength of our study is its large population-based cohort, which allowed full ascertainment of mortality, thereby minimizing misclassification. The use of propensity matching to balance the probability of having a diagnosis of DM on a large number of covariates also reduced potential selection bias in our study. The diagnosis of AF and DM were ascertained through multiple sources including review of medical records, verifying the presence of respective management strategies along with ICD codes to increase the accuracy. The availability of duration of diabetes prior to AF helped us study the effect of duration of diabetes on outcomes. Our study also has some limitations study including its retrospective design, although propensity matching was used to minimize confounding. Ascertainment of DM was based on clinical data. Hence, the presence of diabetes could have been underestimated despite the additional use of laboratory criteria.

In conclusion, the presence of DM and poor glycemic control were both associated with increased risk of mortality in patients with concurrent AF. Improved treatment of DM and CV risk control appear to confer a significant protective effect on survival. Future prospective studies are needed to confirm the reproducibility of our findings.

SOURCES OF FUNDING

Dr. Rowlens Melduni is supported by National Institutes of Health (NIH) K01 (HL 135288).

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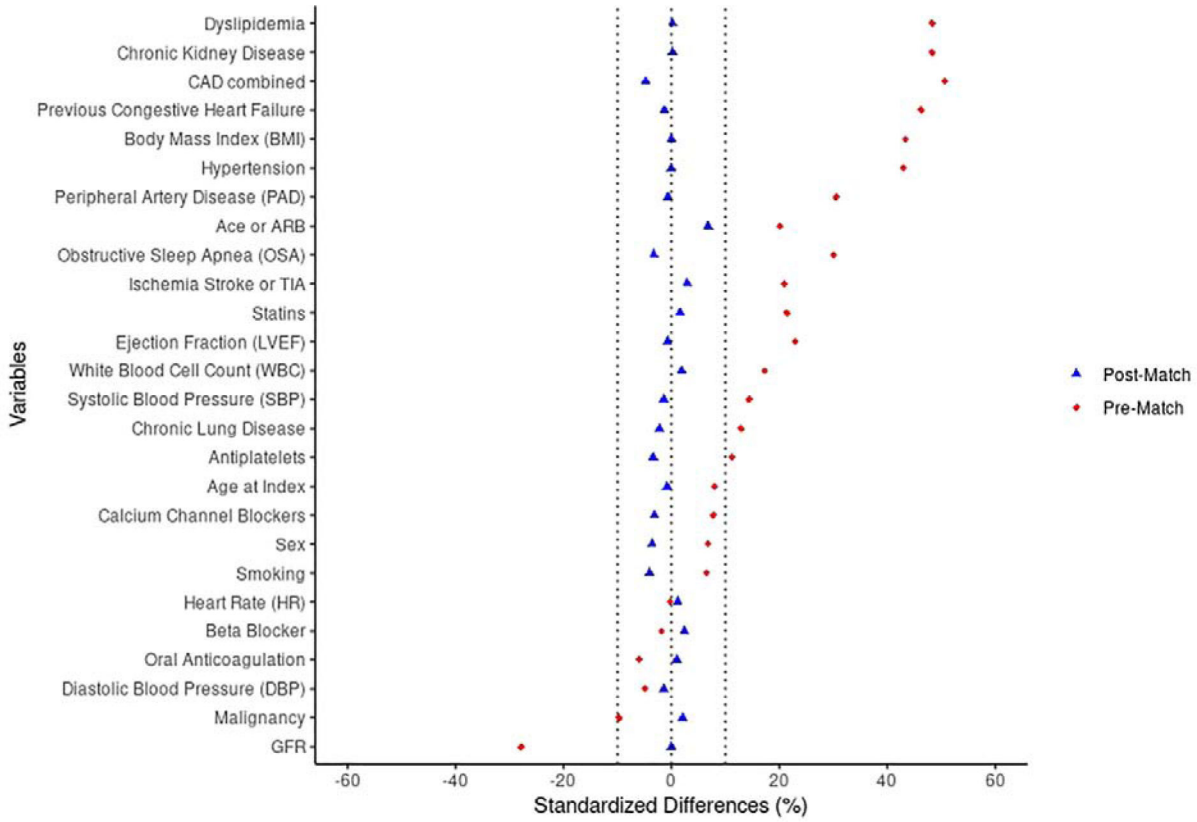

Figure 1. Balance Plot showing standardized differences of baseline variables before and after propensity matching

Abbreviations: CAD: Coronary artery disease; GFR: Glomerular filtration rate

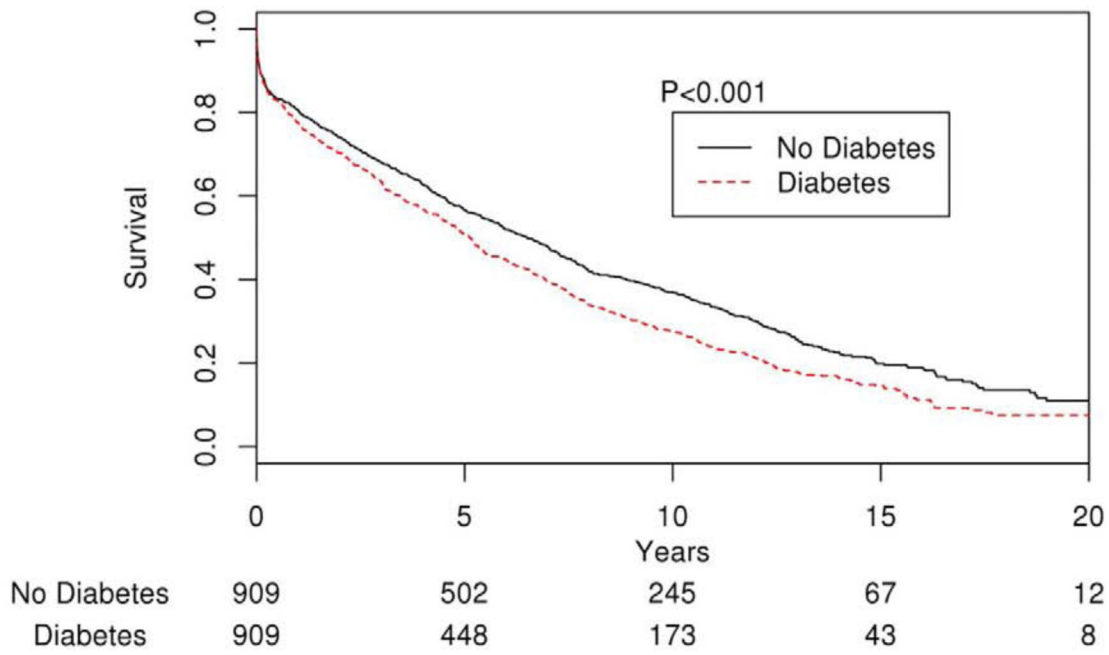

Figure 2.

Kaplan-Meier curve showing survival differences between AF patients with and without diabetes

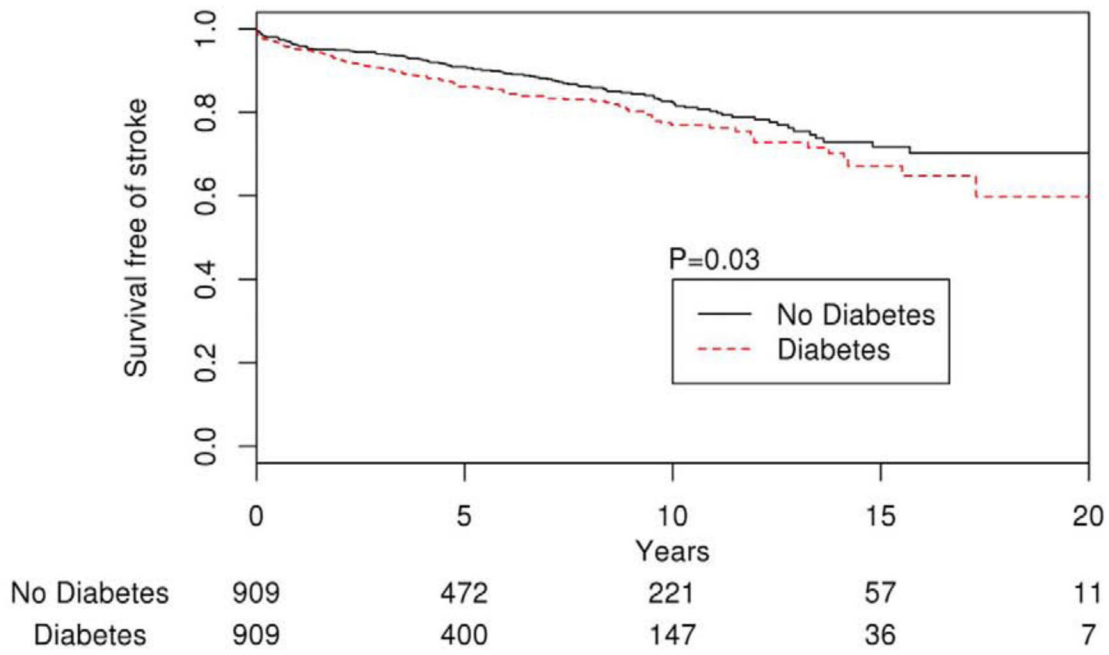

Figure 3.
Kaplan-Meier curve showing stroke-free survival in AF patients with and without diabetes

Table 1.

Baseline characteristics of propensity-score matched cohort of atrial fibrillation stratified by diabetes

Characteristic	Diabetes Mellitus		Overall (n=1818)	P-value
	NO (n=909)	YES (n=909)		
Age, mean (SD) (in years)	74.1 (12.2)	74.0 (10.7)	74.0(11.5)	.29
Men	512(56.3%)	495 (54.5%)	1007 (55.4%)	.42
Body mass index (kg/m^2)	30.2 (7.7)	30.2 (6.7)	30.2 (7.2)	.22
Heart rate (beats per min)	109.3 (32.4)	108.9(31.7)	109.1 (32.0)	.86
Systolic Blood pressure (mmHg)	131.6(22.1)	131.3(21.7)	131.4(21.9)	.70
Diastolic Blood pressure (mmHg)	71.4(14.5)	71.2(14.1)	71.3(14.3)	.88
Hypertension	818(90.0%)	818(90.0%)	1636 (90.0%)	1.00
Dyslipidemia	689 (75.8%)	690(75.9%)	1379 (75.9%)	.96
Coronary Artery Disease	591 (65.0%)	570 (62.7%)	1161 (63.9%)	.30
Heart failure	294 (32.3%)	288(31.7%)	582 (32.0%)	.76
Prior Stroke	179 (19.7%)	201 (22.1%)	380 (20.9%)	.20
Peripheral Arterial Disease	234(25.7%)	231 (25.4%)	465 (25.6%)	.87
Smoker (past or present)	290(31.9%)	273 (30.0%)	563(31.0%)	.39
Chronic lung disease	358 (39.4%)	348 (38.3%)	706 (38.8%)	.63
Obstructive sleep apnea	284(31.2%)	270 (29.7%)	554 (30.5%)	**.47**
Chronic Renal Disease	360 (39.6%)	361 (39.7%)	721 (39.7%)	.96
Malignancy	331 (36.4%)	340 (37.4%)	671 (36.9%)	.66
White blood cell count (1000 per mm^3)	9.4 (5.4)	9.5 (5.3)	9.4 (5.3)	.57
Glomerular filtration rate (ml/min/1.73m^2)	55.9 (26.3)	55.9 (27.5)	55.9 (26.9)	.97
LV ejection fraction (%)	53.8(15.1)	53.7 (15.4)	53.8(15.3)	.89
Statins	515(56.7%)	523(57.5%)	1038(57.1%)	.70
Oral Anticoagulation (Warfarin or NOAC)	482(53.0%)	486(53.5%)	968 (53.2%)	.85
Beta-Blocker	625(68.8%)	635(69.9%)	1260 (69.3%)	.61
Calcium Channel-blocker	452(49.7%)	437(48.1%)	889 (48.9%)	.48
ACE-I or ARB	581(63.9%)	610(67.1%)	1191 (65.5%)	.15
Antiplatelets	251(27.6%)	237(26.1%)	488 (26.8%)	.45

Represented as Number (percentage) or mean (standard deviation)

Abbreviations: LV: left ventricle; ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

Footnote: Dyslipidemia was defined as total cholesterol >200 mg/dl or low-density cholesterol levels >100 mg/dl or high-density cholesterol levels <60 mg/dl

Table 2.
Propensity-score matched Univariate Associations with Mortality

Variable	Hazard Ratio	95% Confidence Interval	P-value
Diabetes mellitus	1.25	1.12 – 1.39	<.001
Men	0.81	0.73 – 0.90	<.001
Age	1.07	1.06 – 1.07	<.001
Body mass index	0.96	0.95 – 0.97	<.001
Systolic blood pressure	1.00	0.99 – 1.00	0.12
Diastolic blood pressure	0.99	0.99 – 0.99	<.001
Mean arterial pressure	0.99	0.99 – 0.99	0.02
Hypertension	1.43	1.18 – 1.73	<.001
Dyslipidemia	0.79	0.70 – 0.90	<.001
Coronary Artery Disease	1.55	1.39 – 1.74	<.001
Congestive heart failure	2.20	1.97 – 2.46	<.001
Cardiomyopathy (Ischemic, idiopathic, hypertrophic, dilated, tachycardia-induced)	1.47	1.27 – 1.69	<.001
Previous valve surgery	1.29	0.94 – 1.79	0.12
Prior Stroke or TIA	1.89	1.67 – 2.14	<.001
Prior GI bleeding	1.43	1.25 – 1.64	<.001
Peripheral Arterial Disease	1.54	1.37 – 1.73	<.001
Smoking (past or present)	1.34	1.20 – 1.49	<.001
Chronic lung disease	1.64	1.47 – 1.83	<.001
Obstructive sleep apnea	0.90	0.80 – 1.01	0.09
Chronic Renal Disease	1.95	1.75 – 2.17	<.001
Dialysis	2.69	2.09 – 3.47	<.001
Thyroid disease	1.20	1.04 – 1.38	0.01
Malignancy	1.63	1.46 – 1.82	<.001
Insulin	0.86	0.74 – 1.00	0.06
Oral hypoglycemic agents	0.61	0.53 – 0.70	<.001
Statins	0.45	0.40 – 0.50	<.001
Oral Anticoagulation (Warfarin or NOAC)	0.49	0.44 – 0.54	<.001
beta-blocker	0.47	0.42 – 0.52	<.001
Calcium Channel-blocker	0.69	0.62 – 0.77	<.001
Digoxin	1.09	0.97 – 1.23	0.15
ACE-I or ARB	0.62	0.55 – 0.69	<.001
Diuretics	0.85	0.76 – 0.96	0.01
Antiplatelets	1.03	0.92 – 1.16	0.58
Antiarrhythmics	0.49	0.41 – 0.58	<.001
CHA_2DS_2-VASc score	1.34	1.30 – 1.37	<.001
White blood cell count	1.03	1.03 – 1.04	<.001

Variable	Hazard Ratio	95% Confidence Interval	P-value
Creatinine	1.26	1.21 – 1.31	<.001
Glomerular filtration rate	0.99	0.99 – 0.99	<.001
Thyroid stimulating hormone	1.02	1.00 – 1.04	0.01
Cardiac index	1.10	1.01 – 1.19	0.02
LA volume index	1.02	1.01 – 1.02	<.001
E/e' ratio	1.04	1.03 – 1.05	<.001
RV systolic pressure	1.03	1.03 – 1.04	<.001
Right atrial pressure	1.09	1.07 – 1.10	<.001
LV ejection fraction	0.98	0.98 – 0.99	<.001
HbA_{1c}	1.07	1.04 – 1.11	<.001

Abbreviations:LA: left atrial; LV: left ventricle; RV: right ventricle

Table 3.
Propensity-score matched Univariate Associations with Stroke

Variable	Hazard Ratio	95% Confidence Interval	P-value
Diabetes mellitus	1.32	1.02 – 1.70	0.03
Men	0.57	0.44 – 0.74	<.001
Age	1.04	1.03 – 1.06	<.001
Body mass index	0.97	0.95 – 0.99	0.001
Systolic Blood pressure	1.01	1.00 – 1.02	<.001
Diastolic Blood pressure	0.99	0.99 – 1.01	0.564
Mean arterial pressure	1.01	0.99 – 1.01	0.18
Hypertension	2.25	1.31 – 3.87	0.003
Dyslipidemia	0.93	0.69 – 1.25	0.62
Coronary Artery Disease	1.06	0.82 – 1.37	0.65
Congestive heart failure	1.22	0.91 – 1.63	0.18
Cardiomyopathy (Ischemic, idiopathic, hypertrophic, dilated, tachycardia-induced)	0.66	0.42 – 1.03	0.07
Previous valve surgery	1.95	0.94 – 4.08	0.07
Prior Stroke or TIA	2.00	1.49 – 2.68	<.001
Prior GI bleeding	0.94	0.65 – 1.36	0.74
Peripheral Arterial Disease	1.28	0.96 – 1.71	0.09
Smoker (past or present)	0.81	0.61 – 1.09	0.16
Chronic lung disease	0.96	0.73 – 1.26	0.75
Obstructive sleep apnea	0.85	0.64 – 1.13	0.25
Chronic Renal Disease	1.13	0.86 – 1.48	0.38
Dialysis	0.67	0.21 – 2.11	0.50
Thyroid disease	1.25	0.90 – 1.75	0.18
Malignancy	1.02	0.78 – 1.34	0.87
Insulin	1.14	0.81 – 1.60	0.44
Oral hypoglycemic agents	1.02	0.77 – 1.36	0.86
Statins	0.88	0.67 – 1.15	0.34
Oral Anticoagulation (Warfarin or NOAC)	1.01	0.78 – 1.32	0.93
beta-Blocker	1.08	0.78 – 1.49	0.63
Calcium Channel-blocker	1.29	1.00 – 1.67	0.05
Digoxin	1.06	0.80 – 1.40	0.70
ACE-I or ARB	1.15	0.85 – 1.54	0.36
Diuretics	1.46	1.05 – 2.02	0.02
Antiplatelets	1.40	1.08 – 1.83	0.01
Antiarrhythmics	0.96	0.70 – 1.32	0.83
CHA_2DS_2-VASc score	1.20	1.13 – 1.28	<.001
White blood cell count	0.98	0.95 – 1.02	0.35

Variable	Hazard Ratio	95% Confidence Interval	P-value
Creatinine	0.92	0.75 – 1.12	0.39
Glomerular filtration rate	1.00	0.99 – 1.01	0.73
Thyroid stimulating hormone	0.97	0.92 – 1.02	0.27
Cardiac index	0.97	0.79 – 1.18	0.74
LA volume index	1.01	0.99 – 1.02	0.07
E/e' ratio	1.05	1.03 – 1.06	<.001
RV systolic pressure	1.02	1.01 – 1.03	0.002
Right atrial pressure	1.05	1.01 – 1.08	0.005
LV ejection fraction	1.00	0.99 – 1.01	0.98
HbA_{1c}	1.04	0.96 – 1.13	0.34

Abbreviations: LA: left atrial; LV: left ventricle; RV: right ventricle