Presence of diabetic microvascular complications does not incrementally increase risk of ischemic stroke in diabetic patients with atrial fibrillation
A nationwide cohort study
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Abstract
Conventional stroke risk prediction tools used in atrial fibrillation (AF) incorporate the presence of diabetes mellitus (DM) as a risk factor. However, it is unknown whether this risk is homogenous or dependent on the presence of diabetic microvascular complications, such as diabetic retinopathy, nephropathy, and neuropathy. The present study examined the risk of ischemic stroke in diabetic patients with and without microvascular complications. The present study used the National Health Insurance Research Database in Taiwan with detailed healthcare data on all-comers to the Taiwanese medical system from January 1, 1996 to December 31, 2011. AF and DM were identified when listed as discharge diagnoses or confirmed more than twice in the outpatient department. Patients on antithrombotic agents were excluded. The clinical endpoint was ischemic stroke. Among the 50,180 AF patients with DM, the majority had no microvascular complications (72.7%), while 2.6% had diabetic retinopathy, 8.4% had diabetic nephropathy, and 16.1% had diabetic neuropathy. Ischemic stroke occurred in 6003 patients, with a 4.74% annual risk of ischemic stroke. When compared with DM patients without microvascular complications, those with diabetic retinopathy, nephropathy, or neuropathy had higher incidences of ischemic stroke (4.65 vs 5.07, 4.77, or 5.20 per 100 person-years, respectively). However, after adjusting for confounding factors, the differences were no longer significant. In a large nationwide AF cohort with DM, risk of ischemic stroke was similar between patients with and without microvascular complications, suggesting that risk stratification of these patients does not require inclusion of diabetic retinopathy, nephropathy, and neuropathy.

Abbreviations: AF=atrial fibrillation, CI=confidence interval, DM=diabetes mellitus, ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification, NHI=National Health Insurance, NHIIRD=National Health Insurance Research Database, NOACs=nonvitamin K antagonists oral anticoagulants, TIA=transient ischemic attack.

Keywords: atrial fibrillation, diabetes mellitus, ischemic stroke, microvascular complications, risk stratification

1. Introduction
Atrial fibrillation (AF) confers a higher risk of ischemic stroke, and this risk substantially increases with the concomitant presence of 1 or more risk factors.[1–3] When compared with non-AF-related strokes, strokes related to AF are associated with greater disability and higher mortality, underscoring the importance of stroke prevention in this population.[1] Prevention of thromboembolism is obtained with antithrombotic therapy, including vitamin K antagonists such as warfarin, and non-vitamin K antagonists oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban.[4–6] The decision to use antithrombotic therapy is reliant on stroke risk prediction tools, of which the most common are the older CHADS2 (congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/transient ischemic attack (TIA)),[7] and the CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74, and sex category female sex) scores.[8] Diabetes mellitus (DM) has been identified by numerous studies as a risk factor of AF.[5,6,9,10] In a meta-analysis of more than 1.6 million subjects, patients with DM had a 39% greater risk of AF compared to nondiabetics, which remained significant after adjusting for other confounding risk factors.[9] DM was also an important risk factor of ischemic stroke in AF patients, and
has been included as a risk component of the common scoring schemes for stroke risk stratification in AF. The development of diabetic microvascular complications (i.e., retinopathy, nephropathy, or neuropathy) reflects more advanced disease[11] and may incrementally predict those with increased DM severity and a higher risk of AF. However, no studies have specifically implicated microvascular complications in stroke risk of diabetic AF patients. In the present study, we aimed to retrospectively examine the risk of ischemic stroke in diabetic AF patients with and without diabetic retinopathy, nephropathy, and/or neuropathy.

2. Methods

2.1. Database

The study protocol of the present study is similar to previous studies.[12–17] The National Health Insurance Research Database (NHIRD) maintained by the Taiwan National Health Research Institute was utilized in this study. The National Health Insurance (NHI) system is a mandatory country-wide program that provides comprehensive medical coverage for all Taiwanese residents. The NHIRD consists of detailed healthcare data from >23 million enrolled patients, representing >99% of Taiwan’s population. In this database, patient identification numbers were encrypted for privacy protection, with consistent encrypting to allow linkage of data belonging to the same patient. Information on comorbid conditions was obtained from medical claims based on the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) codes. Patients were identified to have a specific comorbidity only when it was listed as a discharge diagnosis or confirmed more than twice in the outpatient department. The diagnostic accuracies of important comorbidities in NHIRD, such as hypertension, DM, heart failure, myocardial infarction, hyperlipidemia, and chronic obstructive pulmonary disease have been validated previously.[18,19] The large sample size and longitudinal information of this database provide an optimal platform to examine outcomes of chronic cardiac conditions and associations with comorbidities.

2.2. Study population

From January 1, 1996 to December 31, 2011, a total of 354,649 AF patients aged ≥20 years were identified from the NHIRD. AF was diagnosed using the ICD-9-CM code 427.31. To ensure the accuracy of the diagnosis, we defined patients with AF only when AF was a discharge diagnosis or confirmed more than twice in the outpatient department.[20] The diagnostic accuracy of AF in the NHIRD using this definition has been validated previously.[21,22] The CHA2DS2-VASc score was calculated for each patient by assigning 1 point each for a history of heart failure, hypertension, diabetes, or vascular disease (myocardial infarction or peripheral artery disease), age 65 to 74 years, or female sex, and 2 points each for a history of stroke, transient ischemic attack, or age ≥75 years.[23] Among the study cohort, we excluded patients receiving warfarin or antiplatelet agents, including aspirin, clopidogrel, dipyridamole, and ticlopidine. Patients on an anticoagulant or antiplatelet were excluded to assess true thromboembolic risk.

DM and the presence of microvascular complications were identified based on the ICD-9-CM codes: 250.X for DM, 250.5X for retinopathy, 250.4X for nephropathy, and 250.6X for neuropathy. If more than 1 diabetic complication is present, the condition requiring more visits (i.e., the most prevalent) is used.

2.3. Primary clinical outcome

The clinical endpoint was the occurrence of ischemic stroke, with concomitant imaging studies of the brain, including computed tomography or magnetic resonance imaging. The accuracy of the diagnosis of ischemic stroke in Taiwan’s NHIRD has been reported to be around 94%.[17] Another validation study also demonstrated that the diagnostic accuracy of ischemic stroke in NHIRD was high, with the positive predictive value and sensitivity of 88.4% and 97.3%, respectively.[23]

2.4. Statistical analysis

Data are presented as the mean value and standard deviation for normally distributed continuous variables and proportions for categorical variables. Differences between continuous values were assessed using an unpaired 2-tailed $t$ test for normally distributed variables and Mann–Whitney rank-sum test for skewed variables. Differences between nominal variables were compared by the Chi-squared test. The cumulative incidence curve of ischemic stroke was plotted via the Kaplan–Meier method, with statistical significance examined by the log-rank test. The risk of ischemic stroke was assessed using the Cox regression analysis. All statistical significances were set at $P<0.05$.

The present study was approved by the Institutional Review Board (IRB) at Taipei Veterans General Hospital, Taipei, Taiwan.

3. Results

Of the 354,649 AF patients in the database, 168,079 patients were excluded for anticoagulant or antiplatelet use. Of the remaining patients ($n=186,570$), 50,180 (14.1%) were documented to have DM and comprised the study cohort. The cohort was divided into 4 categories based on the absence of diabetic complications or if present, on the most prevalent diabetic complication: no microvascular complications, diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy. The majority of participants did not have microvascular complications (36,505 patients; 72.7%), while 1311 patients (2.6%) had diabetic retinopathy, 4240 patients (8.4%) had diabetic nephropathy, and 8124 patients (16.1%) had diabetic neuropathy. The patient flow diagram is shown in Fig. 1. Table 1 shows

![Figure 1](image-url). Patient flow diagram. Among 50,180 AF patients with DM not receiving oral anticoagulants or antiplatelet agents, 36,505 (72.7%) had no microvascular complications, 1311 (2.6%) had diabetic retinopathy, 4240 (8.4%) had diabetic nephropathy, and 8124 (16.1%) had diabetic neuropathy. NHIRD = National Health Insurance Research Database, AF = atrial fibrillation, DM = diabetes mellitus.
the baseline characteristics of the study groups. There were significant baseline differences between the four groups in terms of age, sex, CHA2DS2-VASc score, concomitant risk factors, comorbidities, and medications.

The primary outcome occurred in 6003 patients, with an annual risk of 4.74%. The incidence rates of ischemic stroke for diabetic AF patients with or without microvascular complications are shown in Table 2 and the respective cumulative incidence curves are shown in Fig. 2. The risk of ischemic stroke was not significantly higher among patients with diabetic retinopathy or nephropathy compared to patients without complications (Table 3). Patients with diabetic neuropathy were associated with an increased risk of ischemic stroke compared to those without microvascular complications with a hazard ratio of 1.109 (95% confidence interval CI=1.032–1.192, P=0.005) (Table 3). After adjusting for baseline differences, including age, sex, and comorbidities, diabetic neuropathy was no longer significantly associated with an increased risk of ischemic stroke with an adjusted hazard ratio of 1.064 (95% CI=0.984–1.152, P=0.122).

Among 13,675 patients with microvascular complications, 9080 of them had only 1 kind, 3534 had 2 kinds, and 1061 had 3 kinds of complications. Compared to patients without microvascular complications, the risk of ischemic stroke did not differ significantly for patients with 1 or 2 or 3 kinds of microvascular complications (1 kind vs none: adjusted HR=1.017, 95% CI=0.820–1.261, P=0.878; 2 kinds vs none: adjusted HR=1.045, 95% CI=0.840–1.299, P=0.695; 3 kinds vs none: adjusted HR=1.106, 95% CI=0.990–1.235, P=0.076). If we only focused on patients with 1 kind of microvascular complication (n=9080), patients with different kinds of microvascular complications were not associated with an increased risk of ischemic stroke.

### Table 1

| Variables | None (n=36,505) | Retinopathy (n=1311) | Nephropathy (n=4240) | Neuropathy (n=8124) | P |
|-----------|-----------------|----------------------|----------------------|---------------------|---|
| Age, y    | 74.0 ± 11.4     | 72.1 ± 10.4          | 73.3 ± 10.6          | 74.1 ± 10.0         | <0.001 |
| Age ≥ 65 y, n (%) | 29,711 (81.4) | 1015 (77.4) | 3404 (80.3) | 6800 (83.7) | <0.001 |
| Age ≥ 75 y, n (%) | 19,696 (54.0) | 587 (44.8) | 2133 (50.3) | 4371 (53.8) | <0.001 |
| Gender (male), n (%) | 17,862 (48.9) | 643 (49.1) | 2030 (47.9) | 3589 (44.2) | <0.001 |
| CHA2DS2-VASc score, median (IQR) | 5 (4–6) | 5 (4–7) | 6 (4–7) | 6 (5–7) | <0.001 |

### Table 2

| Groups | Number of events | Number of Patients | Person-years | Incidence |
|--------|-----------------|--------------------|--------------|-----------|
| Without microvascular complications | 4544 | 36,505 | 97,678 | 4.65 |
| With microvascular complications | | | | |
| Retinopathy | 154 | 1311 | 3037 | 5.07 |
| Nephropathy | 418 | 4240 | 8770 | 4.77 |
| Neuropathy | 887 | 8124 | 17,066 | 5.20 |
| Total | 6003 | 50,180 | 126,351 | 4.74 |

*Number of ischemic stroke per 100 person-years of follow-up.
ischemic stroke compared to those without any complication (retinopathy vs none: adjusted HR = 1.103, 95% CI = 0.939–1.295, \( P = 0.234 \); nephropathy vs none: adjusted HR = 0.994, 95% CI = 0.890–1.112, \( P = 0.992 \); neuropathy vs none: adjusted HR = 0.988, 95% CI = 0.797–1.225, \( P = 0.912 \)).

Table 3 shows the results of Cox regression models analyzing the risk of ischemic stroke for patients with each microvascular complication compared to those without. When stratified according to the CHA2DS2-VASc score (range 1–9), there were no differences in the adjusted hazard ratios for ischemic stroke for each diabetic complication when compared to no diabetic complication at each score (Fig. 3).

### Table 3

| Models | HR       | 95% CI       | \( P \)  |
|--------|----------|--------------|---------|
| Model 1: unadjusted regression analysis | None | 1 (Reference) |         |
|        | Retinopathy | 1.086 | 0.925–1.276 | 0.312 |
|        | Nephropathy | 1.016 | 0.919–1.124 | 0.752 |
|        | Neuropathy | 1.109 | 1.032–1.192 | 0.005 |
| Model 2: adjusted for age, sex | None | 1 (Reference) |         |
|        | Retinopathy | 1.102 | 0.938–1.294 | 0.238 |
|        | Nephropathy | 1.025 | 0.927–1.134 | 0.626 |
|        | Neuropathy | 1.092 | 1.016–1.174 | 0.017 |
| Model 3: adjusted for age, sex and comorbidities listed in Table 1 | None | 1 (Reference) |         |
|        | Retinopathy | 1.110 | 0.945–1.304 | 0.204 |
|        | Nephropathy | 1.027 | 0.927–1.137 | 0.609 |
|        | Neuropathy | 1.151 | 1.069–1.238 | <0.001 |
| Model 4: adjusted for all variables in model 3, and the use of drugs including ARB, ACEi, thiazides, calcium channel blockers, statins, beta blocker | None | 1 (Reference) |         |
|        | Retinopathy | 1.114 | 0.948–1.309 | 0.190 |
|        | Nephropathy | 1.037 | 0.936–1.149 | 0.490 |
|        | Neuropathy | 1.159 | 1.076–1.248 | <0.001 |
| Model 5: adjusted for all variables in model 3, and the use of drugs listed in Table 1 | None | 1 (Reference) |         |
|        | Retinopathy | 1.045 | 0.888–1.230 | 0.592 |
|        | Nephropathy | 0.974 | 0.876–1.082 | 0.619 |
|        | Neuropathy | 1.064 | 0.984–1.152 | 0.122 |

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II-receptor blocker, CI = confidence interval, HR = hazard ratio.

### 4. Discussion

The close relationship between DM and new-onset AF has been disclosed before. A subgroup analysis of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial demonstrated that new-onset DM was associated with an increased risk of new-onset AF in hypertensive patients.[24] Several studies further investigated the risk of new-onset AF among diabetic patients with or without microvascular complications. In a study by Vischer et al.[25] looking at the consequences of renal insufficiency in elderly hospitalized diabetic patients, nephropathy was associated with a higher risk of AF compared with elderly diabetic patients without nephropathy. In a Turkish cross-sectional, observational study of the prevalence of AF in diabetic patients with and without diabetic autonomic neuropathy, patients with diabetic neuropathy had higher glycosylated hemoglobin A (HbA1c) levels and had a significantly higher rate of AF.[26] The concomitant increase in HbA1c levels and AF prevalence may reflect less optimal diabetic control or more advanced disease resulting in a higher risk of AF or may conversely be explained by the proarrhythmic effects of autonomic imbalance from diabetic neuropathy.[27] Although these previous studies have demonstrated that the presence of diabetic microvascular complications was associated with a high prevalence of AF, the relationship between microvascular complications and risk of ischemic stroke among AF patients with DM is less clear. The present study is the first nationwide
investigation with a large number of nonanticoagulated AF patients with DM. Despite the postulation that diabetic end-organ damage reflects more advanced DM, we demonstrated that patients with and without diabetic complications had similar rates of ischemic stroke after adjusting for confounding variables. In this study, the presence of diabetic retinopathy, diabetic nephropathy, or diabetic neuropathy did not pertain a higher risk of ischemic stroke beyond that demonstrated by the presence of DM alone. Even at higher CHA2DS2-VASc scores, the presence of a diabetic complication did not increase the risk of ischemic stroke. Interestingly, although the ATRIA (anticoagulation and risk factors in atrial fibrillation) study, which enrolled >10,000 AF patients, found a graded, increasing risk of thromboembolism associated with the impaired renal function, we did not observe an increased risk of ischemic stroke for diabetic AF patients with diabetic nephropathy compared to those without microvascular complications. Since the detailed data about estimated glomerular filtration rate were not available from Taiwan’s NHIRD, we were not able to further clarify the severity of renal dysfunction for patients with diabetic nephropathy. Therefore, whether AF patients with advanced diabetic nephropathy had a higher risk of ischemic stroke remained unclear based on the results were presented here.

4.1. Clinical implications

Decisions on the use of anticoagulation for stroke prevention in AF should be based on the balance of stroke reduction against major bleeding and a higher risk of stroke should favor the use of antithrombotic agents. In the present study, we demonstrated that the stroke risks of diabetic patients with and without diabetic complications are similar and there is no incremental increase in risk with more end-organ damage. Based on our findings, the current stroke risk prediction tools, such as the CHA2DS2-VASc score, do not require modification to account for the presence of diabetic complications.

4.2. Study limitations

A strength of our study involves the use of a nationwide database with a large sample of subjects. However, there remain limitations to our study, mainly because of its retrospective nature. First, the types of AF (paroxysmal or nonparoxysmal) were not available from this nationwide dataset. Although the risk of stroke did not differ between patients with paroxysmal or nonparoxysmal AF in previous studies, the recent analyses of ACTIVE-A/AVERROES databases showed that the risk of ischemic stroke was higher in patients with nonparoxysmal AF.
compared to those with the paroxysmal type. However, neither the current American nor the current European guidelines recommend identification of the AF type for the decision on the use of oral anticoagulants. Second, the diagnoses of AF and DM, and the occurrence of ischemic stroke were based on the diagnostic codes registered by the physicians responsible for the management of patients; nonetheless, the accuracy of diagnosis of AF, DM, and ischemic stroke in Taiwan’s NHIRD has been previously validated. Also, it should be noted that the accurate and reliable information about the types of diabetes (type 1 or type 2) was not available in this registry database, and therefore we did not perform analyses for patients with type 1 and type 2 diabetes separately. However, type 2 diabetes should theoretically account for the majority of the study patients given the mean age of the study population was older than 70 years. Third, although the average CHA2DS2-VASc score was high, our cohort of patients was not on anticoagulation and the reason could not be identified via our methods. This may represent a higher-risk population with a greater propensity for bleeding, but regardless, it allows us to compare the different study groups. Fourth, although the length of each comorbidity may potentially impact the risk of stroke, it is difficult to ascertain the time sequence and duration of each microvascular comorbidities, which often can be diagnosed late into the condition. A recent study has demonstrated that the duration of diabetes is a more important predictor of ischemic stroke than glycemic control in patients who have diabetes and AF. A further study is important predictor of ischemic stroke than glycemic control in which often can be diagnosed late into the condition. A recent sequence and duration of each microvascular comorbidities, where such information is also elusive. diabetic complications. This mirrors the real-world population neuropathy, precluding direct correlation of ischemic stroke with diabetic retinopathy, diabetic nephropathy, or diabetic ischemic stroke. Lastly, the database does not distinguish diabetes, presence of microvascular complications, and risk of ischemic stroke. Likewise, the database does not distinguish between diabetic retinopathy, diabetic neuropathy, or diabetic neuropathy from other causes of retinopathy, nephropathy, or neuropathy, precluding direct correlation of ischemic stroke with diabetic complications. This mirrors the real-world population where such information is also elusive.

5. Conclusions

In this real-world nationwide nonanticoagulated AF cohort with DM, the risk of ischemic stroke was similar between diabetic patients with no microvascular complications and those with diabetic retinopathy, nephropathy, or neuropathy, indicating that risk stratification of these patients does not require inclusion of diabetic microvascular complications.

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