Long-Term Risks of Stroke in Patients With Type A Aortic Dissection: A Nationwide Cohort Study

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BACKGROUND: Patients with type A aortic dissection (TAAD) have a high short-term risk of stroke. However, whether patients with TAAD have an increased long-term risk of stroke is still undetermined, and our study aims to address this knowledge gap.

METHODS AND RESULTS: A nationwide retrospective cohort study was conducted using Taiwan’s National Health Insurance Research Database. We included patients with TAAD as well as age- and sex-matched aortic disease–free individuals between 2003 and 2016. Inverse probability of treatment weighting was performed to balance patient characteristics between the groups. The primary outcome was the development of stroke, regardless of subtype; the secondary outcomes were the risk of developing either ischemic or hemorrhagic stroke. The hazard ratios (HRs) of stroke were estimated using the Cox proportional hazards model. After inverse probability of treatment weighting, 3556 and 7023 patients were categorized into the TAAD and aortic disease–free cohorts, respectively. The mean follow-up period was 5.71 years. The HRs for overall, ischemic, and hemorrhagic strokes in the TAAD cohort were 3.01 (95% CI, 2.40–3.78), 3.18 (95% CI, 2.47–4.10), and 2.32 (95% CI, 1.58–3.41), respectively, compared with the aortic disease–free cohort. Consistent trends of higher stroke risk in patients with TAAD were revealed in the analyses stratified by age; sex; antiplatelet use; and history of hypertension, diabetes, or dyslipidemia.

CONCLUSIONS: Our study findings revealed that patients with TAAD had an increased long-term risk of both ischemic and hemorrhagic strokes. Further studies are warranted to establish optimal strategies for stroke prevention in these patients.

Key Words: hemorrhagic stroke, ischemic stroke, stroke, type A aortic dissection

Type A aortic dissection (TAAD) is one of the most life-threatening cardiovascular diseases. With advances in surgical repair techniques in recent years, the 3-year survival rate of patients with TAAD has increased to 90.5%. However, TAAD is associated with an increased risk of in-hospital stroke, mainly related to aortic arch vessel involvement and intramural hematoma from the dissection site of the aorta. The International Registry of Acute Aortic Dissection stated that 6% of patients with TAAD presented with stroke on hospital admission.

The long-term risk of stroke in patients with TAAD remains unclear. TAAD affects not only vascular fragility but also vessel remodeling; both mechanisms were found to be associated with atherosclerosis in recent studies. Vascular fragility might cause the vascular endothelium to develop vessel injuries, which is the first step toward atherosclerosis. Vessel remodeling is also an important process for atherosclerosis, particularly atherosclerotic plaque healing. Atherosclerosis of the small vessels in the brain increases the risk of ischemic stroke and intracerebral hemorrhage. Moreover, a high prevalence rate of intracranial aneurysms has also been noted in patients with TAAD. A previous study showed an increased risk of subarachnoid hemorrhage in patients with aortic disease.
According to the aforementioned information, it is reasonable to assume that patients with TAAD are associated with a higher long-term risk of stroke than the general population; however, to date there is little evidence regarding this issue.

Our study aims to investigate whether patients with TAAD have an increased long-term risk of stroke based on nationwide longitudinal data in Taiwan.

**METHODS**

Taiwan’s National Health Insurance Research Database (NHIRD) is maintained and regulated by the Health and Welfare Data Science Center at the Ministry of Health and Welfare in Taiwan. The data set could only be used in the division of the Health and Welfare Data Science Center. Researchers who are interested in analyzing this data set can request access to the Taiwan Ministry of Health and Welfare (https://dep.mohw.gov.tw/DOS/cp-2516-3591-113.html).

**Study Design, Data Source, and Ethical Approval**

We conducted a nationwide cohort study using Taiwan’s NHIRD between 2000 and 2017. The NHIRD is drawn from the electronic claims data of the Taiwan National Health Insurance program, a mandatory single-payer program that comprises >99% of the Taiwanese population, approximately 23.6 million individuals. The NHIRD is currently regulated and stored by the Health and Welfare Data Science Center of Taiwan’s Ministry of Health and Welfare. These data are only approved for analysis by the Division of the Health and Welfare Data Science Center in Taiwan. The NHIRD is an anonymized database comprising comprehensive health care data, including inpatient, outpatient, emergency visits, surgery procedures, and detailed prescription medication data. All information for an individual could be linked and followed longitudinally using an encrypted identification number. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes before 2016 and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes after 2016 were used as the diagnostic and procedural codes.

The study protocol was approved by the Institutional Review Board of Hualien Tzu Chi Hospital (IRB107-152-C). This study was performed in accordance with the Declaration of Helsinki; informed consent was waived because the Taiwan NHIRD is an encrypted research database.

The index date for patients with TAAD was defined as the date of discharge from hospitalization; an identical date was set as the index date for the 1:2 age- and sex-matched aortic disease-free individuals. All patients with a history of stroke, cerebral aneurysm, or related cerebral vascular disease (ICD-9 430–438 or ICD-10 I60–I69) before the index date were excluded to avoid bias. Incidences of death or stroke during the hospitalization for TAAD and age <20 years or lack of complete basic information were the exclusion criteria. We further conducted stabilized inverse probability of treatment weighting (IPTW) to construct a pseudo population to balance the potential differences in baseline characteristics between patients with TAAD and aortic disease-free individuals after age- and sex-matching.

**CLINICAL PERSPECTIVE**

What Is New?

- Type A aortic dissection was associated with a higher long-term risk of strokes, including ischemic and hemorrhagic strokes.
- This trend of increased risk of stroke was consistent across subgroups stratified by age; sex; antiplatelet use; and history of hypertension, diabetes, or dyslipidemia.

What Are the Clinical Implications?

- These findings may provide physicians with more evidence of the need for intensive follow-up and aggressive risk factor control for modifiable stroke risk factors in patients with type A aortic dissection.
- Further studies are warranted to establish optimal strategies for stroke prevention in these patients.

**Nonstandard Abbreviations and Acronyms**

| Abbreviation | Definition |
|--------------|------------|
| IPTW         | inverse probability of treatment weighting |
| NHIRD        | National Health Insurance Research Database |
| TAAD         | type A aortic dissection |

**Study Population**

We included all patients diagnosed with TAAD from January 1, 2003, to December 31, 2016. Patients with TAAD were defined as those diagnosed with aortic dissection (International Classification of Diseases, Ninth Revision [ICD-9] 441.0 and International Classification of Diseases, Tenth Revision [ICD-10] I71.0) who underwent surgical repair of the ascending aorta or aortic arch, depending on the surgical codes. Individuals without a diagnosis of aortic disease (ICD-9 441.x or ICD-10 I71.x) were enrolled into the aortic disease-free cohort in this study.

The NHIRD is an anonymized database comprising comprehensive health care data, including inpatient, outpatient, emergency visits, surgery procedures, and detailed prescription medication data. All information for an individual could be linked and followed longitudinally using an encrypted identification number. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes before 2016 and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes after 2016 were used as the diagnostic and procedural codes.

The study protocol was approved by the Institutional Review Board of Hualien Tzu Chi Hospital (IRB107-152-C). This study was performed in accordance with the Declaration of Helsinki; informed consent was waived because the Taiwan NHIRD is an encrypted research database.
Outcomes
The primary outcome was defined as an inpatient diagnosis of stroke, including both stroke subtypes (ischemic and hemorrhagic), which was further confirmed by brain imaging examination. The diagnostic criteria for stroke have been validated in the Taiwan NHIRD. The diagnostic codes of ischemic stroke were ICD-9-CM codes 433, 434, and 436 and ICD-10-CM codes I63 and I67.89, and the codes of hemorrhagic stroke were ICD-9-CM codes 430 and 431 and ICD-10-CM codes I60 and I61. The follow-up period was initiated from the index date and ended with either the occurrence of stroke, death, withdrawal from the insurance system, or December 31, 2017, whichever came first. With regard to the secondary outcome, we separately analyzed the risk of stroke subtype, either ischemic or hemorrhagic. To estimate the stroke risk, we compared patients with TAAD with aortic disease–free individuals.

Covariates
All comorbidities listed in Table 1 were dependent on the diagnostic codes regarding any inpatient diagnosis or at least 2 outpatient diagnoses. We used a minimum 3-year trace-back period to identify these comorbidities. The income level was estimated based on insurance premiums. The Charlson Comorbidity Index was calculated according to comorbidities. Preexisting medication use was defined using drug prescription data with a duration of ≥30 days within 1 year before the index date. Antiplaetelet use was defined as receiving any antiplaetelet drug during the follow-up period. In addition, the connective tissue disorder included Marfan’s syndrome and Ehlers–Danlos syndrome, which were considered to display an association between aortic dissection and connective tissue disorder.

Statistical Analysis
We calculated propensity scores to estimate the probability of patients being assigned to the TAAD and aortic disease–free cohorts via a logistic regression model; the model included age, sex, income level, Charlson Comorbidity Index, the comorbidities listed in Table 1, preexisting medication use, and antiplaetelet use. Stabilized IPTW using the propensity score was then performed to create a weighted pseudo population, increasing the comparability of the 2 cohorts before the analyses. We examined the difference in the baseline characteristics according to the value of the standardized difference; the value of <0.1 was considered a negligible difference. The probability of stroke between the 2 cohorts was shown using the Kaplan–Meier curves, and the difference between the 2 curves was examined using the log-rank test. The association between risk of stroke and TAAD was evaluated using a univariable Cox proportional hazards model that estimates the hazard ratios (HRs) and corresponding 95% CIs. We also performed stratified analyses based on age; sex; history of hypertension, diabetes, or dyslipidemia; and antiplaetelet use. Statistical significance was defined as a 2-tailed probability value of <0.05. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC) and Stata version 14 (Stata Corporation LLC, College Station, TX).

RESULTS
Baseline Characteristics
After 1:2 matching according to age and sex, the TAAD and aortic disease–free cohorts comprised 3520 patients and 7040 patients, respectively. Their baseline characteristics demonstrated a mean age of 55.1 years and male predominance. Compared with aortic disease–free individuals, patients with TAAD had a higher proportion of hypertension; atrial fibrillation; coronary artery disease; chronic kidney disease; valvular heart disease; connective tissue disorder; and preexisting angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, and diuretic medication use. Moreover, the patients with TAAD displayed a lower proportion of diabetes and the use of metformin compared with the aortic disease–free individuals (Table S1). After IPTW, the TAAD and aortic disease–free cohorts included 3556 and 7023 patients, respectively, with comparable baseline characteristics (Table 1). The mean follow-up period was 5.32 and 5.91 years in the TAAD and aortic disease–free cohorts, respectively.

Risk of Overall Stroke, Ischemic Stroke, and Hemorrhagic Stroke
The Kaplan–Meier curves revealed a higher overall risk of stroke (Figure – Panel A), ischemic stroke (Figure – Panel B), and hemorrhagic stroke (Figure – Panel C) in the TAAD cohort, and the log-rank test revealed significant differences (overall stroke, P<0.001; ischemic
stroke, \( P<0.001 \); hemorrhagic stroke, \( P<0.001 \). In the TAAD and aortic disease–free cohorts, 187 and 130 patients developed strokes, respectively. The Cox proportional hazards models revealed higher risks of overall stroke (HR, 3.01 [95% CI, 2.40–3.78]; \( P<0.001 \)), ischemic stroke (HR, 3.18 [95% CI, 2.47–4.10]; \( P<0.001 \)), and hemorrhagic stroke (HR, 2.32 [95% CI, 1.58–3.41]; \( P<0.001 \)) (Table 2) in the TAAD cohort.

### Stratified Analysis Based on Age, Sex, Hypertension, Diabetes, Dyslipidemia, and Antiplatelet Drug Use

Overall, a statistically higher risk of stroke in patients with TAAD was revealed by the analyses stratified by age; sex; antiplatelet drug use; and history of hypertension, diabetes, or dyslipidemia (Table 3). Table S2

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**Table 1. Baseline Characteristics After the Inverse Probability of Treatment Weighting**

|                      | TAAD cohort (n=3556) | Aortic disease–free cohort (n=7023) | Standardized difference |
|----------------------|----------------------|------------------------------------|-------------------------|
| **Age, y**           |                      |                                    |                         |
| Age<55               | 1645 (46.3)          | 3281 (46.7)                        | 0.009                   |
| Age≥55               | 1910 (53.7)          | 3743 (53.3)                        | 0.009                   |
| **Mean\(^a\)**       | 55.8 (12.3)          | 55.5 (12.3)                        | 0.020                   |
| **Sex**              |                      |                                    |                         |
| Male                 | 2562 (72.0)          | 5096 (72.6)                        | 0.012                   |
| Female               | 994 (28.0)           | 1927 (27.4)                        | 0.012                   |
| **Income level (NTD)** |                    |                                    |                         |
| Dependence           | 224 (6.3)            | 439 (6.2)                          | 0.003                   |
| 15,840–24,999        | 853 (24.0)           | 1698 (24.2)                        | 0.004                   |
| 25,000–39,999        | 1226 (34.5)          | 2426 (34.5)                        | 0.001                   |
| ≥40,000              | 1252 (35.2)          | 2460 (35.0)                        | 0.004                   |
| Charlson Comorbidity Index\(^a\) | 0.5 (1.0)          | 0.5 (1.1)                          | 0.007                   |
| **Comorbidities**    |                      |                                    |                         |
| Hypertension         | 1067 (30.0)          | 2106 (30.0)                        | 0.001                   |
| Diabetes             | 362 (10.2)           | 662 (9.4)                          | 0.026                   |
| Dyslipidemia         | 443 (12.5)           | 813 (11.6)                         | 0.027                   |
| Atrial fibrillation  | 30 (0.8)             | 73 (1.0)                           | 0.021                   |
| Coronary artery disease | 281 (7.9)           | 539 (7.7)                          | 0.009                   |
| Peripheral arterial occlusion disease | 18 (0.5) | 41 (0.6) | 0.011 |
| Cirrhosis            | 65 (1.8)             | 121 (1.7)                          | 0.008                   |
| Chronic kidney disease | 154 (4.3)           | 297 (4.2)                          | 0.005                   |
| Major gastrointestinal bleeding | 22 (0.6)    | 51 (0.7) | 0.014 |
| Malignancy           | 117 (3.3)            | 231 (3.3)                          | 0.001                   |
| Valvular heart disease | 27 (0.8)            | 61 (0.9)                           | 0.012                   |
| Connective tissue disorder\(^\dagger\) | 30 (0.8) | 0 (0) | 0.130 |

**Preexisting medication use\(^\ddagger\)**

|                      |                      |                                    |                         |
| ACEI and ARB         | 682 (19.2)           | 1321 (18.8)                        | 0.009                   |
| β-blocker            | 586 (16.5)           | 1132 (16.1)                        | 0.010                   |
| Diuretic             | 248 (7.0)            | 470 (6.7)                          | 0.011                   |
| Metformin            | 215 (6.1)            | 401 (5.7)                          | 0.015                   |
| Statin               | 338 (9.5)            | 617 (8.8)                          | 0.025                   |

**Medication use during the follow-up**

|                      |                      |                                    |                         |
| Antiplatelet use     | 1338 (37.6)          | 1332 (19.0)                        | 0.423                   |

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*Data are expressed as number (percentage) unless indicated otherwise. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NTD, new Taiwan dollar; and TAAD, type A aortic dissection.

\(^a\)Expressed as mean (SD).

\(^\dagger\)Connective tissue disorder refers to the Marfan’s syndrome or the Ehlers–Danlos syndrome. We could not enter connective tissue disorder into the variables of the logistic regression while calculating propensity score to balance the baseline characteristics and hemorrhagic stroke.

\(^\ddagger\)Preexisting medication use refers to a drug prescription for at least 30 days within 1 year before the index date.

\(^\dagger\)Antiplatelet use refers to any exposure of antiplatelet treatment during the observation period.
shows the detailed information for the number of events and the incidence rate in each subgroup.

Sensitivity Analyses

We also performed 3 sensitivity analyses that demonstrated consistent findings. In sensitivity analysis A, TAAD was associated with a higher risk of overall stroke (adjusted HR, 3.33 [95% CI, 2.60–4.25]; \(P<0.001\)) as well as ischemic stroke (adjusted HR, 3.44 [95% CI, 2.62–4.51]; \(P<0.001\)) and hemorrhagic stroke (adjusted HR, 2.61 [95% CI, 1.71–3.97]; \(P<0.001\)) (Table 4). Sensitivity analyses B and C also robust our primary analysis and detailed information disclosed in Table 4.

DISCUSSION

This cohort study showed that patients with TAAD had an increased long-term risk of stroke when compared with aortic disease–free individuals. Patients with TAAD were associated with a >3-fold higher risk of stroke compared with aortic disease–free individuals for a mean follow-up period of \(\approx 5.71\) years. The results of the stratified analyses also demonstrated similar findings. To our knowledge, this is the first cohort study to examine the association between the long-term risk of stroke and TAAD.

Although previous studies have already demonstrated an association between an increased short-term risk of stroke in patients with TAAD, the data used were primarily collected from the health care information during hospitalization in either hospital-based or registry-based cohorts.\(^5\)–\(^7\) The International Registry of Acute Aortic Dissection collected the largest global TAAD cohort and provided valuable data for the long-term outcomes of mortality and reoperation rates. However, the results of these studies did not disclose much information on the long-term risk of stroke.\(^23\),\(^24\) Nationwide population-based claims data might be one of the most appropriate tools to evaluate the association with the long-term risk of stroke in patients with TAAD.\(^25\) Claims data provided valuable information regarding not only long-term outcomes, such as the development of death and stroke, but also preexisting comorbidities.\(^16\) Those data helped us adjust most of the risk factors related to stroke and competing risk for death in patients with TAAD. Therefore, we believed that our data fulfilled the knowledge gaps regarding long-term outcomes, which was an inherent limitation of registry-based data.

Patients with TAAD appeared to have an association with genetic defects in vessel remodeling, which may negatively affect the homeostasis of vessel

Table 2. Risk of Stroke in Patients With TAAD Compared With That in Aortic Disease–Free Individuals After the Inverse Probability of Treatment Weighting

| Outcome        | TAAD cohort (n=3556) | Aortic disease–free cohort (n=7023) | HR\(^\dagger\) (95% CI) | \(P\) value |
|----------------|----------------------|-------------------------------------|------------------------|-------------|
| Overall stroke | 187                  | 9.87                                | Event                  | 130         | 3.14        | 3.01 (2.40–3.78) | <0.001       |
| Ischemic stroke| 156                  | 8.23                                | Event                  | 102         | 2.45        | 3.18 (2.47–4.10) | <0.001       |
| Hemorrhagic stroke | 88              | 3.00                                | Event                  | 50          | 1.21        | 2.32 (1.58–3.41) | <0.001       |

HR indicates hazard ratio; IR, incidence rate; and TAAD, type A aortic dissection.
\(\dagger\)IR per 1000 person-years.
\(\dagger\)HRs were calculated using a univariable Cox proportional hazard regression model.
regeneration, particularly with regard to atherosclerotic plaque healing. The pathological hypothesis of atherosclerotic plaque healing has recently gained attention. Physicians might, in the future, obtain an alternative method to explore disease association and develop a potential therapeutic intervention for atherosclerosis. Patients with TAAD often have genetic defects in extracellular matrix proteins, the inhibitory pathway for matrix metalloproteinase via TGF-β, transforming growth factor β, or smooth muscle contraction proteins. During the process of atherosclerotic plaque healing, the stabilization of vessel homeostasis depends on TGF-β, type I and type III collagen, and smooth muscle cell progenitors. In the mechanism of TAAD, previous studies revealed the increased expression of type I collagen, type III collagen, and TGF-β on the surgical specimen of the aortic wall of patients with thoracic aortic dissection. Therefore, Wang et al hypothesized that compromised distensibility may have resulted in the overexpression of these extracellular matrix proteins and cytokines. We hypothesized that an increased risk of ischemic stroke in patients with TAAD might be associated with defects in atherosclerotic plaque healing, and further fundamental research may provide more evidence to elucidate this pathological mechanism. In hemorrhagic stroke, atherosclerosis is also associated with the development of intracerebral hemorrhage, particularly in the transition zone of the cerebral vessels from the main vessel to the small vessel. Moreover, vascular fragility might decrease vascular compliance to resist blood pressure and result in the development of an intracranial aneurysm and rupture of the cerebral aneurysm, particularly in patients with uncontrolled hypertension. Al-Kawaz et al demonstrated an association with an increased risk of subarachnoid hemorrhage in patients with aortic disease, but the subgroup analysis disclosed inconsistent findings. The association of an increased risk of subarachnoid hemorrhage might exist only in patients with nonruptured aortic aneurysms, and not in patients with ruptured aortic aneurysms or aortic dissections. Our data revealed that patients with TAAD had a 2-fold higher risk of developing hemorrhagic stroke, including subarachnoid hemorrhage. Our study filled the knowledge gap concerning the risk of stroke in patients with TAAD and raised the question of which preventive strategy for stroke could benefit these patients.

In our TAAD cohort, patients with TAAD displayed a higher proportion of valvular heart disease and a lower proportion of diabetes and metformin use. Kim et al demonstrated that patients with both acute aortic dissection and mitral valvular disease were associated with a higher risk of atherosclerosis than those without mitral valvular disease. Both Avdic et al and He et al

### Table 3. Stratified Analyses to Assess the Risk of Stroke in Patients With TAAD Compared With Aortic Disease–Free Individuals

| Characteristic     | HR*   | 95% CI   | P value |
|--------------------|-------|----------|---------|
| Age, y             |       |          |         |
| <55                | 4.86  | 3.21–7.36| <0.001  |
| ≥55                | 2.41  | 1.82–3.19| <0.001  |
| Sex                |       |          |         |
| Male sex           | 2.65  | 2.03–3.48| <0.001  |
| Female sex         | 3.73  | 2.48–5.67| <0.001  |
| Hypertension       |       |          |         |
| Yes                | 2.22  | 1.58–3.11| <0.001  |
| No                 | 3.97  | 2.86–5.52| <0.001  |
| Diabetes           |       |          |         |
| Yes                | 1.98  | 1.07–3.68| 0.030   |
| No                 | 3.34  | 2.59–4.30| <0.001  |
| Dyslipidemia       |       |          |         |
| Yes                | 2.33  | 1.33–4.10| 0.003   |
| No                 | 3.10  | 2.41–3.98| <0.001  |
| Antipatelet use†   |       |          |         |
| Yes                | 2.39  | 1.63–3.50| <0.001  |
| No                 | 4.09  | 3.07–5.44| <0.001  |

HR indicates hazard ratio; and TAAD, type A aortic dissection.
*HRs were calculated using the aortic disease–free cohort as the reference group in the univariable Cox proportional hazard regression model.
†Antiplatelet use was defined as a drug prescription for >1 day during the observation period.

### Table 4. Sensitivity Analyses A, B, and C: Risk of Stroke in Patients With TAAD Compared With That in Aortic Disease–Free Individuals

|                      | HR   | 95% CI   | P value |
|----------------------|------|----------|---------|
| Sensitivity analysis A*| 3.33 | 2.60–4.25| <0.001  |
| Ischemic stroke      | 3.44 | 2.62–4.51| <0.001  |
| Hemorrhagic stroke   | 2.61 | 1.71–3.97| <0.001  |
| Sensitivity analysis B†| 3.02 | 2.40–3.79| <0.001  |
| Ischemic stroke      | 3.19 | 2.47–4.11| <0.001  |
| Hemorrhagic stroke   | 2.32 | 1.58–3.42| <0.001  |
| Sensitivity analysis C‡| 2.75 | 2.18–3.48| <0.001  |
| Ischemic stroke      | 2.91 | 2.23–3.78| <0.001  |
| Hemorrhagic stroke   | 2.11 | 1.42–3.12| <0.001  |

HR indicates hazard ratio; and TAAD, type A aortic dissection.
*Sensitivity analysis A was performed for all eligible cases (without inverse probability of treatment weighting) using a multivariable Cox proportional hazards model. The model was adjusted for age, sex, income level, Charlson Comorbidity Index, the comorbidities listed in Table 1, preexisting medication use, and antiplatelet use.
†Sensitivity analysis B was performed for the inverse probability of treatment weighting cohorts using a univariable Cox proportional hazards regression model after excluding all patients with a connective tissue disorder and their corresponding aortic disease–free comparators.
‡Sensitivity analysis C was performed for the inverse probability of treatment weighting cohorts using a univariable Fine–Gray proportional subdistribution hazards model.
mentioned that a history of diabetes was associated with a lower risk of developing acute aortic dissection, which may have attributed to a lower proportion of diabetes in our TAAD cohort. Previous research only mentioned the risk of mortality in patients with both TAAD and diabetes; however, the risk of stroke or atherosclerosis in these patients was seldom mentioned. Prakash et al reported that patients with TAAD and a history of diabetes were negatively correlated with the risk of mortality compared with those without a history of diabetes. In addition, metformin use may display an association with a lower growth rate of aortic aneurysms. The possible mechanism may involve the anti-inflammatory and vascular-protective effects of metformin to preclude the inflammation of the aorta and reduce extracellular matrix remodeling. Overall, both valvular disease and diabetes with or without metformin use may be the risk factors for allocation imbalance to each cohort or the potential confounders for stroke development. Thus, we entered these factors into the logistic regression model while calculating the propensity score to adjust for their potential confounding effects.

This study has some inherent limitations. First, some confounding factors related to stroke may not be considered or adjusted in our analyses. The Taiwan NHIRD is an administrative claims database that does not contain all stroke risk factors, such as body mass index, history of alcohol or cigarette use, diet, and physical habits. Therefore, some unmeasured or unknown confounding factors may have been present in our study and bias the results. Second, the severity of stroke may have a socioeconomic implication; however, we could not obtain the information for stroke severity from the Taiwan NHIRD, thus necessitating further studies to investigate this issue considering the severity of stroke. Third, this association may not be generalizable to other countries or populations. There may exist some inherent genetic differences, such as a relatively higher prevalence of intracerebral dissection in the Asian population than that in the European population. More studies from diverse populations are required to confirm this association.

In conclusion, we determined that patients with TAAD had a long-term increased risk of stroke, both ischemic and hemorrhagic. Similar findings were obtained in analyses that were stratified by age, sex, antiplatelet drug use; and history of hypertension, diabetes, or dyslipidemia. These findings may provide physicians with more evidence regarding the need for intensive follow-up and aggressive risk factor control for modifiable stroke risk factors in patients with TAAD. Further randomized control trials are necessary to determine the optimal preventive strategies for stroke in these patients.

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Disclosures
None.

Supplemental Material
Tables S1–S2

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| Table S1. Baseline characteristics before the inverse probability of treatment weighting |
|-----------------------------------------------|
|                                              |
|                                              |
| **Age, years**                               |
| (n=3,520)                                    |
| TAAD                                         |
| Aortic disease-free                         |
| Standardized Difference                     |
|                                              |
|                                              |
| **<55**                                      |
| 1,692 (48.0)                                 |
| 3,384 (48.0)                                 |
| 0.000                                        |
|                                              |
| **≥55**                                      |
| 1,828 (52.0)                                 |
| 3,656 (52.0)                                 |
| 0.000                                        |
|                                              |
| **Sex**                                      |
|                                              |
| **Male**                                     |
| 2,550 (72.4)                                 |
| 5,100 (72.4)                                 |
| 0.000                                        |
|                                              |
| **Female**                                   |
| 970 (27.6)                                   |
| 1,940 (27.6)                                 |
| 0.000                                        |
|                                              |
| **Income level (NTD)**                       |
|                                              |
| **Dependence**                               |
| 189 (5.4)                                    |
| 461 (6.6)                                    |
| 0.050                                        |
|                                              |
| **15,840─24,999**                            |
| 890 (25.3)                                   |
| 1,670 (23.7)                                 |
| 0.036                                        |
|                                              |
| **25,000─39,999**                            |
| 1,303 (37.0)                                 |
| 2,345 (33.3)                                 |
| 0.078                                        |
|                                              |
| **≧40,000**                                  |
| 1,138 (32.3)                                 |
| 2,564 (36.4)                                 |
| 0.086                                        |
|                                              |
| **Charlson comorbidity index**†              |
| 0.5 (1.0)                                    |
| 0.4 (0.9)                                    |
| 0.154                                        |
|                                              |
| **Comorbidities**                            |
|                                              |
| **Hypertension**                             |
| 1,650 (46.9)                                 |
| 1,539 (21.9)                                 |
| 0.546                                        |
|                                              |
| **Diabetes mellitus**                        |
| 201 (5.7)                                    |
| 774 (11.0)                                   |
| 0.192                                        |
|                                              |
| **Dyslipidemia**                             |
| 394 (11.2)                                   |
| 823 (11.7)                                   |
| 0.016                                        |
|                                              |
| **Atrial fibrillation**                      |
| 59 (1.7)                                     |
| 26 (0.4)                                     |
| 0.130                                        |
|                                              |
| **Coronary artery disease**                  |
| 404 (11.5)                                   |
| 368 (5.2)                                    |
| 0.227                                        |
|                                              |
| **Peripheral arterial occlusion disease**    |
| 28 (0.8)                                     |
| 25 (0.4)                                     |
| 0.058                                        |
|                                              |
| **Chronic kidney disease**                   |
| 108 (3.1)                                    |
| 78 (1.1)                                     |
| 0.137                                        |
|                                              |
| **Cirrhosis**                                |
| 130 (3.7)                                    |
| 309 (4.4)                                    |
| 0.036                                        |
|                                              |
| **Major gastrointestinal bleeding**          |
| 29 (0.8)                                     |
| 41 (0.6)                                     |
| 0.029                                        |
|                                              |
| **Malignancy**                               |
| 117 (3.3)                                    |
| 211 (3.0)                                    |
| 0.018                                        |
|                                              |
| **Valvular heart disease**                   |
| 66 (1.9)                                     |
| 13 (0.2)                                     |
| 0.169                                        |
|                                              |
| **Connective tissue disorder**†              |
| 42 (1.2)                                     |
| 0 (0.0)                                      |
| 0.155                                        |
|                                              |
| **Pre-existing medication use‡**             |
|                                              |
| **ACEI and ARB**                             |
| 508 (26.3)                                   |
| 754 (9.8)                                    |
| 0.440                                        |
|                                              |
| **Beta-blocker**                             |
| 507 (26.2)                                   |
| 640 (8.3)                                    |
| 0.489                                        |
|                                              |
| **Diuretics**                                |
| 205 (10.6)                                   |
| 201 (2.6)                                    |
| 0.327                                        |
|                                              |
| **Metformin**                                |
| 44 (2.3)                                     |
| 395 (5.1)                                    |
| 0.150                                        |
|                                              |
| **Statin**                                   |
| 130 (6.7)                                    |
| 497 (6.4)                                    |
| 0.012                                        |
|                                              |
| **Medication use during the follow-up**      |
|                                              |
| **Antiplatelet use§**                        |
| 695 (36.0)                                   |
| 1,009 (13.1)                                 |
| 0.553                                        |
Data are expressed as n (%) unless otherwise indicated.

*Expressed as mean (SD)

†Connective tissue disorder refers to Marfan’s syndrome or Ehlers-Danlos syndrome.

‡Pre-existing medication use refers to a drug prescription for at least 30 days within one year prior to the index date.

§Antiplatelet use refers to any exposure of antiplatelet treatment during the observation period.

Abbreviations: NTD, New Taiwan dollar; TAAD, type A aortic dissection; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker.
Table S2. Detailed information of the stratified analyses to assess the risk of stroke in patients with TAAD compared to aortic disease-free individuals

| Subgroup | Group          | Case number | Event | Incidence rate* |
|----------|----------------|-------------|-------|-----------------|
| **Age**  |                |             |       |                 |
| < 55     | TAAD           | 1,705       | 76    | 7.87            |
|          | Aortic disease-free | 3,372      | 34    | 1.61            |
|          | TAAD           | 1,838       | 105   | 11.33           |
|          | Aortic disease-free | 3,658      | 96    | 4.63            |
| ≥ 55     | TAAD           | 2,583       | 129   | 9.41            |
|          | Aortic disease-free | 5,085      | 97    | 3.26            |
|          | TAAD           | 982         | 58    | 10.95           |
|          | Aortic disease-free | 1,936      | 37    | 3.09            |
| **Sex**  |                |             |       |                 |
| Male     | TAAD           | 1,681       | 107   | 12.82           |
|          | Aortic disease-free | 1,512      | 49    | 5.81            |
|          | TAAD           | 1,875       | 86    | 8.35            |
|          | Aortic disease-free | 5,499      | 69    | 2.06            |
| Female   | TAAD           | 201         | 15    | 15.78           |
|          | Aortic disease-free | 776        | 33    | 7.85            |
|          | TAAD           | 3,335       | 167   | 9.28            |
|          | Aortic disease-free | 6,255      | 101   | 2.69            |
| **Hypertension** | | | | |
| Yes      | TAAD           | 399         | 25    | 12.82           |
|          | Aortic disease-free | 815        | 24    | 5.63            |
|          | TAAD           | 3,141       | 159   | 9.46            |
|          | Aortic disease-free | 6,200      | 107   | 2.88            |
| No       | TAAD           | 1,354       | 78    | 10.56           |
|          | Aortic disease-free | 1,176      | 40    | 4.82            |
|          | TAAD           | 2,195       | 113   | 9.81            |
|          | Aortic disease-free | 5,851      | 80    | 2.40            |

Data are expressed as n (%) unless otherwise indicated.

*Incidence rate per 1,000 person-years

Abbreviations: DM, diabetes mellitus; TAAD, type A aortic dissection