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Stroke occurrence while on antiplatelet therapy may predict atrial fibrillation detected after stroke

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HIGHLIGHTS

- A breakthrough stroke is an ischemic stroke despite treatment with antiplatelets.
- Early detection of atrial fibrillation (AF) is essential in stroke patients without known AF.
- A breakthrough stroke of mild severity may predict AF detected after stroke.
- Patients with a breakthrough stroke are recommended for cardiac monitoring.

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ABSTRACT

Background and aims: Stroke occurrence while on antiplatelet therapy, i.e., a breakthrough stroke, is often conveniently attributed to antiplatelet resistance. However, undetected paroxysmal atrial fibrillation (AF) may underlie breakthrough strokes. We hypothesized that a breakthrough stroke may be a clinical marker for patients at risk of having AF detected after stroke (AFDAS).

Methods: Consecutive patients without known AF hospitalized for ischemic stroke between 2000 and 2013 were identified from nationwide claims data. The independent variable of interest was continued use of antiplatelet therapy within 30 days before stroke. The diagnosis of AF and comorbidities were ascertained using validated algorithms. Stroke severity (National Institutes of Health Stroke Scale [NIHSS]) was estimated using a validated claims-based method. Univariable and multivariable Cox regression analyses were used to determine the effect of breakthrough strokes on the occurrence of AFDAS separately in patients with mild and severe stroke (estimated NIHSS ≤ 10 *versus* > 10).

Results: Among 17,076 patients (40% female, mean age 69 years), 3314 (19%) were on antiplatelet therapy before stroke. In patients with mild stroke, prior antiplatelet use was significantly associated with the occurrence of AFDAS (adjusted hazards ratio, 1.26; 95% confidence interval, 1.08–1.48). In contrast, no association existed between prior antiplatelet use and the risk of AFDAS in those with severe stroke.

Conclusions: Patients with a breakthrough stroke of mild severity while on antiplatelet therapy carried an increased risk of AFDAS compared to those not on antiplatelet therapy. Our findings may help prioritize patients for advanced cardiac monitoring in daily practice.

1. Introduction

Antiplatelet therapy is the mainstay of acute treatment and secondary prevention for cardiovascular ischemic events including ischemic stroke. However, some patients still experience ischemic stroke despite treatment with antiplatelet therapy. Such circumstances are often referred to as “aspirin treatment failure” [1] or, more broadly, as “antiplatelet treatment failure” [2], and the term “breakthrough stroke” has been coined to refer to these strokes [3,4]. A meta-analysis indicated that switching to or adding alternative antiplatelet agents may

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reduce the risk of future major adverse cardiovascular events including stroke in patients with a breakthrough stroke while on aspirin monotherapy [5]. Laboratory antiplatelet resistance, i.e., the laboratory evidence of inadequate inhibition of platelet aggregation by antiplatelet agents in vitro, is a major cause of antiplatelet treatment failure [2], and the mechanisms behind antiplatelet resistance are complex and multifactorial [4].

Nonetheless, before ascribing a breakthrough stroke to antiplatelet resistance and rushing into adjusting antiplatelet regimen, it is paramount to identify the correct mechanism of stroke [4]. Antiplatelet agents are not a panacea to prevent all kinds of ischemic stroke. Antiplatelet therapy clearly has little or no role for stroke prevention in patients with atrial fibrillation (AF) [6]. In addition, antiplatelet therapy may be ineffective in cases of cryptogenic stroke or embolic stroke of unknown source because undetected paroxysmal AF underlies a substantial proportion of these cases [7]. In fact, it was estimated that sequential phases of cardiac monitoring could identify AF detected after stroke (AFDAS) in approximately one fourth of stroke patients without a prior history of AF [8]. Furthermore, no treatment with oral anticoagulation and late diagnosis of AF after ischemic stroke could lead to a doubling risk of stroke recurrence [9]. Consequently, a complete diagnostic workup to identify the underlying mechanism of stroke is essential because the mechanism dictates the best preventive strategy [10].

Currently, a considerable number of studies have been devoted to the discovery of clinical markers and the development of risk prediction scores to stratify the risk of AFDAS in stroke patients without known AF [11]. These clinical markers and prediction scores may help prioritize stroke patients for advanced cardiac monitoring. Because undetected paroxysmal AF is a potential cause of breakthrough strokes, we hypothesized that patients with a breakthrough stroke while on antiplatelet therapy may carry a higher risk of AFDAS than stroke patients not on antiplatelet therapy. In the present study, we aimed to test this hypothesis using data from a nationwide representative sample of patients with ischemic stroke.

2. Materials and methods

2.1. Data source

Taiwan's National Health Insurance is a single-payer, universal, and mandatory health care program which covers virtually all of its residents. The National Health Insurance Research Database (NHIRD) is composed of all inpatient/outpatient claims, prescription claims, and demographic data from the National Health Insurance program. The data underlying this study was obtained from a subset of the NHIRD, the Longitudinal Health Insurance Database 2000 (LHID2000), which contains the data from 1997 to 2013 of one million enrollees randomly sampled in the year 2000. Because the database consists of only de-identified information, this study was exempt from a full review by the Institutional Review Board of Ditmanson Medical Foundation Chiayi Christian Hospital (CYCH-IRB No. 2018020) and informed consent was deemed unnecessary.

2.2. Study group

We selected the first hospitalization for ischemic stroke for each patient between Jan 2000 and Dec 2013 from the LHID2000 based on the principal discharge diagnosis code (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis codes 433.xx and 434.xx) [12,13]. We defined the admission date as the index date. Patients who were diagnosed with AF (ICD-9-CM code 427.31) or received oral anticoagulants in any inpatient or outpatient claims before the index date were excluded. Patients younger than 20 years of age and those without claims items in the database were also eliminated. The remaining patients comprised the study group (Supplemental Fig. 1).

2.3. Outcome event

The event of interest was AFDAS after the index date. The diagnosis of AF was ascertained if an ICD-9-CM code of 427.31 was listed in the secondary discharge diagnosis of the stroke hospitalization, or in at least one subsequent inpatient claims, or at least two subsequent outpatient claims [14]. The earliest date of documented AF was considered the onset of AFDAS. All patients were traced until the onset of AFDAS, death, disenrollment from the NHI, or 31 December 2013, whichever came first. AFDAS was further categorized into early or late, depending on whether the first AF episode occurred within the index hospitalization or beyond the index hospitalization.

2.4. Variables

We retrieved demographic information, diagnosis codes, and prescription data from the LHID2000. The independent variable of interest was continued use of antiplatelet therapy within 30 days before the index date [3]. Antiplatelet medications were identified from the prescription claims. If patients received aspirin, ticlopidine, clopidogrel, or a combo drug containing any of these, they were assigned to the group of patients on antiplatelet therapy and, otherwise, to the group of patients not on antiplatelet therapy. In addition, for sensitivity analysis, we included patients who received dipyridamole or cilostazol in the group of patients on antiplatelet therapy. Comorbidities were ascertained using validated algorithms [14] based on ICD-9-CM diagnosis codes (Supplemental Table 1) from the inpatient and outpatient claims in the one-year lookback period before the index date. Because cardiothoracic surgery (ICD-9-CM procedure codes 30–37) or other major surgery like digestive surgery (ICD-9-CM procedure codes 42–54) may increase the risk of new-onset AF [15,16], operations within one year before the index date were also identified.

2.5. Stroke severity

Because the LHID2000 did not contain information on stroke severity, we used a validated method to estimate stroke severity. The estimated stroke severity has been shown to highly correlate with admission National Institutes Health Stroke Scale (NIHSS) in patients with ischemic stroke [17] and those with hemorrhagic stroke [18]. In brief, seven claims items from the claims for the stroke hospitalization were used to calculate the stroke severity index [17]. The stroke severity index was then converted to the NIHSS using the equation: estimated NIHSS = $1.1722 \times \text{SSI} - 0.7533$ [19]. The estimated NIHSS was then categorized into mild (≤ 10) or severe (> 10) stroke [20].

2.6. Reference group

In order to compare the risk of new-onset AF between patients on antiplatelet therapy in the study group and those hospitalized for reasons other than ischemic stroke but on antiplatelet therapy, we selected the first hospitalization for patients who were not hospitalized for ischemic stroke between Jan 2000 and Dec 2013. Following a similar algorithm, patients who were previously diagnosed with AF or younger than 20 years were excluded. Only patients who had continued use of antiplatelet therapy within 30 days before the index data were retained. Patients who received oral anticoagulants before the index date were eliminated. The remaining patients comprised the reference group (Supplemental Fig. 2).

2.7. Statistical analysis

We reported continuous variables with means and standard deviations, and categorical variables with counts and percentages. Comparisons between groups were made using t tests for continuous variables and chi-square tests for categorical variables. We first

Table 1
Characteristics of the study group.

	Patients on antiplatelet therapy (n = 3314)	Patients not on antiplatelet therapy (n = 13762)	*p*
Age, mean (SD)	71.3 (10.5)	68.2 (12.8)	< 0.001
Female	1246 (37.6)	5569 (40.5)	0.002
Hypertension	2906 (87.7)	9985 (72.6)	< 0.001
Diabetes mellitus	1609 (48.6)	5178 (37.6)	< 0.001
Hyperlipidemia	1241 (37.4)	4163 (30.2)	< 0.001
Coronary artery disease	1411 (42.6)	2127 (15.5)	< 0.001
Congestive heart failure	468 (14.4)	1001 (7.3)	< 0.001
Rheumatic heart disease	71 (2.1)	204 (1.5)	0.007
Cardiomyopathy	26 (0.8)	71 (0.5)	0.065
Chronic kidney disease	184 (5.6)	531 (3.9)	< 0.001
Chronic obstructive pulmonary disease	512 (15.4)	1783 (13.0)	< 0.001
Peripheral artery disease	256 (7.7)	513 (3.7)	< 0.001
Hyperthyroidism	20 (0.6)	84 (0.6)	0.964
Prior ischemic stroke	1113 (33.6)	1166 (8.5)	< 0.001
Prior intracerebral hemorrhage	58 (1.8)	231 (1.7)	0.774
Prior transient ischemic attack	265 (8.0)	339 (2.5)	< 0.001
Prior cardiothoracic surgery	29 (0.9)	121 (0.9)	0.971
Prior digestive surgery	135 (4.1)	604 (4.4)	0.407
Stroke severity			0.307
Estimated NIHSS ≤10	2605 (78.6)	10705 (77.8)	
Estimated NIHSS > 10	709 (21.4)	3057 (22.2)	

Data are numbers (percentage) unless specified otherwise.
NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

analyzed all stroke patients in the study group as a whole. Then patients with different stroke severity were analyzed separately because greater stroke severity may increase the chance of AFDAS [21,22]. For each category of stroke severity, event rates in patients on antiplatelet therapy and those not on antiplatelet therapy were calculated by dividing the number of events by the number of person-years of follow-up. The Kaplan-Meier method was used to plot survival curves stratified by the status of antiplatelet therapy, and differences were assessed by the log-rank test. Cox proportional hazards models were used to assess the association between antiplatelet therapy and the occurrence of AFDAS. In addition to univariable analyses, we performed multivariable analyses in which adjustment was made for potential confounders including age, sex, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, rheumatic heart disease, cardiomyopathy, chronic kidney disease, chronic obstructive pulmonary disease, peripheral artery disease, hyperthyroidism, prior ischemic stroke, prior intracerebral hemorrhage, prior transient ischemic attack, prior cardiothoracic surgery, and prior digestive surgery [23,24]. After fitting the model, the assumption of proportional hazards was assessed with the Schoenfeld test.

We did additional analyses to compare the risk of new-onset AF between patients on antiplatelet therapy in the study group and those in the reference group. The Kaplan-Meier method and multivariable Cox proportional hazards models were used in the same way. Two-tailed *p* values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata 15.1 (StataCorp, College Station, Texas).

3. Results

We identified 19,042 patients hospitalized for ischemic stroke between 2000 and 2013. After excluding those who did not meet the study criteria (Supplemental Fig. 1), the remaining 17,076 patients (40% female, mean age 69 years) comprised the study population. Around 78% of patients had mild stroke (estimated NIHSS ≤10). Overall, 3314 (19%) patients received continuous antiplatelet therapy within 30 days before stroke, including 3049 users of single antiplatelet therapy (aspirin in 2742, ticlopidine in 155, and clopidogrel in 152) and 265 users of dual or triple antiplatelet therapy. Table 1 gives the baseline characteristics between patients on antiplatelet therapy and those not on antiplatelet therapy. Patients on antiplatelet therapy were older, more likely to be male, and generally had more comorbidities than those not on antiplatelet therapy. However, stroke severity was not significantly different between groups.

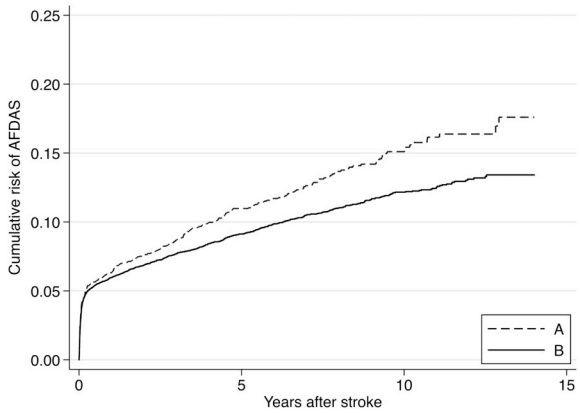

Fig. 1. Cumulative risk of the occurrence of atrial fibrillation detected after stroke (AFDAS).
The *p* value of the log-rank test was 0.001. (A) Patients on antiplatelet therapy; (B) patients not on antiplatelet therapy.

Fig. 1 illustrates the Kaplan-Meier curves for the occurrence of AFDAS. Patients on antiplatelet therapy had a higher cumulative risk of AFDAS than those not on antiplatelet therapy (log-rank test, $p = 0.001$). Fig. 2 illustrates the Kaplan-Meier curves for patients stratified by stroke severity and the status of antiplatelet therapy. Patients with severe stroke (estimated NIHSS > 10) had a higher cumulative risk of AFDAS than those with mild stroke (estimated NIHSS ≤10). The risk of AFDAS was higher in patients on antiplatelet therapy versus those not on antiplatelet therapy for mild stroke (log-rank test, $p < 0.001$), whereas the risk was similar between patients with antiplatelet therapy and those without antiplatelet therapy for severe stroke ($p = 0.646$).

In patients on antiplatelet therapy, 368 developed AFDAS, with 133 (36.1%) detected within the index hospitalization. In patients not on

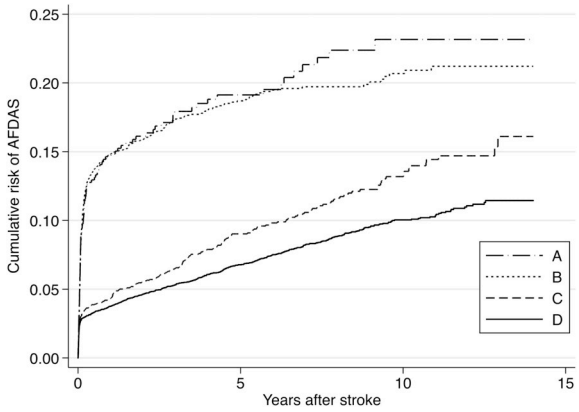

Fig. 2. Cumulative risk of the occurrence of atrial fibrillation detected after stroke (AFDAS).
Overall *p* value of the log-rank test was < 0.001. (A) Severe stroke, patients on antiplatelet therapy; (B) severe stroke, patients not on antiplatelet therapy; (C) mild stroke, patients on antiplatelet therapy; (D) mild stroke, patients not on antiplatelet therapy.

antiplatelet therapy, 1241 were diagnosed with AFDAS, with 528 (42.5%) detected within the index hospitalization. Table 2 shows the crude and adjusted hazard ratios of AFDAS. In all stroke patients studied, a significant association of prior antiplatelet therapy with AFDAS was observed. However, the assumption of proportional hazards was not satisfied. Realizing that the risk of AFDAS may vary with different stroke severity, we analyzed patients with mild and severe stroke separately. In patients with mild stroke, both the univariable and multivariable Cox regression analyses showed that prior antiplatelet use was significantly associated with the occurrence of AFDAS. In contrast, no association existed between prior antiplatelet use and the risk of AFDAS in those with severe stroke. The Schoenfeld tests showed no evidence that the assumption of proportional hazards had been violated. In the sensitivity analysis where patients who received dipyridamole or cilostazol were included in the group of patients on antiplatelet therapy, the results were not materially changed (Supplemental Table 2).

A total of 3269 patients who were hospitalized for reasons other than ischemic stroke but on antiplatelet therapy comprised the reference group. Supplemental Table 3 compares the baseline characteristics between patients on antiplatelet therapy in the study group and the reference group. Patients hospitalized for ischemic stroke had a higher cumulative risk of new-onset AF than those hospitalized for other reasons (Supplemental Fig. 3). The multivariable Cox regression analysis found that patients hospitalized for ischemic stroke were more likely to develop new-onset AF (adjusted hazards ratio, 1.75; 95% confidence interval, 1.46–2.11). The Schoenfeld tests showed that the assumption of proportional hazards was met ($p = 0.167$).

4. Discussion

This study demonstrated that among patients with mild ischemic stroke, those who developed a breakthrough stroke while on antiplatelet therapy were more likely to have AFDAS than those not on antiplatelet therapy. The relationship of breakthrough strokes to the occurrence of AFDAS remained independent after adjustment for common risk factors for new-onset AF. In contrast, despite with an even higher risk of AFDAS, no such relationship was observed between breakthrough strokes and AFDAS in patients with severe ischemic stroke.

4.1. Relationship between AFDAS and breakthrough strokes

AFDAS literally denotes all kinds of AF detected after stroke. It may be either previously undetected AF that is diagnosed by cardiac monitoring after stroke or truly post-stroke new-onset AF including neurogenic AFDAS triggered by stroke [11]. Stimulation of the autonomic system or direct damage to the heart due to post-stroke inflammation, as well as autonomic dysfunction secondary to stroke-related damage to brain regions regulating the autonomic system (e.g., insular cortex) are possible mechanisms behind AFDAS, in particular in patients without underlying structural heart disease [25].

While the reasons why the effect of breakthrough strokes on the occurrence of AFDAS was modified by stroke severity are not clear, we suggest the following explanations for this observation: First, although stroke due to AF was traditionally considered of greater stroke severity [26], low-burden atrial fibrillation, such as short-lasting paroxysmal AF, may produce small thrombi and thus result in stroke of mild severity [11]. Short-lasting paroxysmal AF could also escape from detection until patients are hospitalized for stroke. Consequently, previously undetected paroxysmal AF, rather than post-stroke new-onset AF, might be more represented among patients with AFDAS in the group with mild stroke, in particular among patients with breakthrough strokes because antiplatelet therapy is not effective for prevention of stroke due to AF. Second, patients with severe stroke are more likely to have neurogenic AFDAS because large brain lesion, including those involving the insular cortex, may cause dysautonomia with resulting stroke-induced heart injury [27,28]. In addition, high-burden AF, which generally causes severe stroke, is less likely to escape from detection prior to stroke. As a result, AFDAS in patients with severe stroke might consist of mainly new-onset AF rather than previously undetected paroxysmal AF and, therefore, the status of antiplatelet therapy was not associated with the occurrence of AFDAS.

4.2. Clinical implications

Even though various kinds of cardiac monitoring techniques, either applied in the inpatient or ambulatory setting, can increase the

Table 2
Risk of atrial fibrillation detected after stroke between patients on antiplatelet therapy and those not on antiplatelet therapy.

	No. of events	No. of person-years	Event rate (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
All (n = 17076)					
On antiplatelet therapy	368	17419	21.1	1.21 (1.08–1.36)	1.18 (1.04–1.34)
Not on antiplatelet therapy	1241	70207	17.7	1	1
p for the Schoenfeld test				0.023	< 0.001
Estimated NIHSS ≤10 (n = 13310)					
On antiplatelet therapy	251	14804	17.0	1.32 (1.15–1.52)	1.26 (1.08–1.48)
Not on antiplatelet therapy	769	59429	12.9	1	1
p for the Schoenfeld test				0.189	0.092
Estimated NIHSS > 10 (n = 3766)					
On antiplatelet therapy	117	2615	44.7	1.05 (0.86–1.28)	1.09 (0.88–1.36)
Not on antiplatelet therapy	472	10778	43.8	1	1
p for the Schoenfeld test				0.194	0.233

CI, confidence interval; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale.

detection rate of AF after ischemic stroke [8], universal use of advanced cardiac monitoring for all stroke patients may be costly and infeasible in the real world. Considering the need for appropriate and efficient allocation of medical resources, a number of candidate markers and several risk scores have been proposed to improve the accuracy of predicting AFDAS [11]. However, many of the markers and risk scores require further diagnostic workup such as serum testing [29,30] and imaging analysis [29,31], leading to additional effort and cost in identifying at-risk patients. Simple risk scores based on readily available demographic and medical history may be preferred for routine clinical use [22].

A practical implication of this study is that the adjusted risk of AFDAS was increased by 26% by a history of prior use of antiplatelet therapy among patients with mild ischemic stroke (estimated NIHSS $\leq$10). In other words, advanced cardiac monitoring may have a higher diagnostic yield in mild stroke patients with a breakthrough event than those without. Because the risk of AFDAS is higher in patients with greater stroke severity [21,22], advanced cardiac monitoring may be considered for every patient with severe stroke if no obvious cause of stroke can be identified. In contrast, the cost-effectiveness of advanced cardiac monitoring is likely to be much lower for patients with mild stroke. Under such circumstances, the status of prior antiplatelet therapy may help prioritize patients with mild stroke for advanced cardiac monitoring.

Whether patients with AFDAS have a different risk profile for recurrent ischemic events compared to those with known AF before stroke and those with sinus rhythm is still controversial [32,33], particularly considering that AFDAS may comprise distinct AF phenotypes [11]. One study found no difference in the risk of recurrent ischemic stroke between stroke patients with AFDAS and those with sinus rhythm [34], whereas others showed an increased risk of recurrent risk or transient ischemic attack in AFDAS versus sinus rhythm [9,35]. The inconsistent findings of existing literature may be partly due to the varied study designs and the different time frames used to define AFDAS. Nevertheless, oral anticoagulation should be started in patients with ischemic stroke once AF is detected according to the current guidelines [36,37].

4.3. Study limitations

This study has the following limitations. First, antiplatelet use was defined by prescription claims and it is impossible to determine the compliance of antiplatelet therapy using claims data. Noncompliance is a common cause of antiplatelet resistance [2], which may end up with a breakthrough stroke. However, if we had been able to determine patient compliance and had assigned noncompliant patients to the group of non-users, the effect of breakthrough strokes on the occurrence of AFDAS would have been more significant because strokes in these patients were less likely to be AF-related. Second, the definition AFDAS was based on the ICD-9-CM code. Although the diagnosis code for atrial fibrillation has been validated in the NHIRD claims data [14], we were unable to categorize atrial fibrillation as either chronic or paroxysmal. Besides, the risk of AFDAS was underestimated and much lower than those in clinical trials [38,39] because continuous cardiac monitoring is infrequently used in the real-world setting [9]. Third, there are well-established data suggesting that cerebrovascular risk reduction associated with aspirin use appears to be directly related to the level of C-reactive protein [40]. However, laboratory data are unavailable in administrative claims data and, therefore, we could not include the level of C-reactive protein in the analysis. Finally, we cannot exclude the possibility that the absence of statistically significant association between severe breakthrough strokes and AFDAS was due to inadequate detection of events. Analysis of data from prior studies investigating continuous cardiac monitoring or future prospective studies may be warranted to confirm the findings of this study.

4.4. Conclusions

Among patients with mild ischemic stroke, those having a breakthrough stroke while on antiplatelet therapy carried an increased adjusted risk of AFDAS compared to those not on antiplatelet therapy. In contrast, the status of antiplatelet therapy before stroke was not associated with the occurrence of AFDAS in patients with severe ischemic stroke. A breakthrough stroke of mild severity can be viewed as a clinical marker for patients at risk of having AFDAS. These findings may help prioritize patients for advanced cardiac monitoring to early identify those who need anticoagulation in daily practice.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Cheng-Yang Hsieh: study concept and design, analysis and interpretation, drafting of manuscript, and critical revision of the manuscript for important intellectual content. Cheng-Han Lee: analysis and interpretation, and critical revision of the manuscript for important intellectual content. Sheng-Feng Sung: study concept and design, acquisition of data, analysis and interpretation, drafting of manuscript, critical revision of the manuscript for important intellectual content, and study supervision.

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Appendix A. Supplementary data

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References

[1] F. Shahid, C.A.A. Chahal, M.J. Akhtar, Aspirin treatment failure: is this a real phenomenon? A review of the aetiology and how to treat it, JRSM Short Rep. 4 (2013) 30–39.
[2] M.A. Topcuoglu, E.M. Arsava, H. Ay, Antiplatelet resistance in stroke, Expert Rev. Neurother. 11 (2011) 251–263.
[3] M. Lee, Y.-L. Wu, J.L. Saver, H.-C. Lee, J.D. Lee, K.-C. Chang, et al., Is clopidogrel better than aspirin following breakthrough strokes while on aspirin? A retrospective cohort study, BMJ Open 4 (2014) e006672.
[4] S. John, I. Katzan, Recurrent stroke while on antiplatelet therapy, Neurol. Clin. 33 (2015) 475–489.
[5] M. Lee, J.L. Saver, K.-S. Hong, N.M. Rao, Y.-L. Wu, B. Ovbiagele, Antiplatelet regimen for patients with breakthrough strokes while on aspirin: a systematic review and meta-analysis, Stroke 48 (2017) 2610–2613.
[6] P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, et al., 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with

EACTS, Eur. Heart J. 37 (2016) 2893–2962.
[7] T. Sanna, P.D. Ziegler, F. Crea, Detection and management of atrial fibrillation after cryptogenic stroke or embolic stroke of undetermined source, Clin. Cardiol. 135 (2018) e146.
[8] L.A. Sposato, L.E. Cipriano, G. Saposnik, E. Ruíz Vargas, P.M. Riccio, V. Hachinski, Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis, Lancet Neurol. 14 (2015) 377–387.
[9] G.Y.H. Lip, T.D. Hunter, M.E. Quiroz, P.D. Ziegler, M.P. Turakhia, Atrial fibrillation diagnosis timing, ambulatory ECG monitoring utilization, and risk of recurrent stroke, Circ. Cardiovasc. Qual. Outcomes 10 (2017) e002864.
[10] X. Ustrell, M. Tagawa, Some light in the shadows of atrial fibrillation and stroke: to look or not to look, Neurology 89 (2017) 1536–1537.
[11] J.O. Cerasuolo, L.E. Cipriano, L.A. Sposato, The complexity of atrial fibrillation newly diagnosed after ischemic stroke and transient ischemic attack: advances and uncertainties, Curr. Opin. Neurol. 30 (2017) 28–37.
[12] C.-L. Cheng, Y.-H.Y. Kao, S.-J. Lin, C.-H. Lee, M.-L. Lai, Validation of the national health insurance research database with ischemic stroke cases in Taiwan, Pharmacoepidemiol. Drug Saf. 20 (2011) 236–242.
[13] C.-Y. Hsieh, C.-H. Chen, C.-Y. Li, M.-L. Lai, Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database, J. Formos. Med. Assoc. 114 (2015) 254–259.
[14] S.-F. Sung, C.-Y. Hsieh, H.-J. Lin, Y.-W. Chen, Y.-H.K. Yang, C.-Y. Li, Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or intracerebral hemorrhage in an administrative claims database, Int. J. Cardiol. 215 (2016) 277–282.
[15] N. Echahidi, P. Pibarot, G. O'Hara, P. Mathieu, Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery, J. Am. Coll. Cardiol. 51 (2008) 793–801.
[16] T. Yoshida, S. Uchino, T. Yokota, T. Fujii, S. Uezono, M. Takinami, The impact of sustained new-onset atrial fibrillation on mortality and stroke incidence in critically ill patients: a retrospective cohort study, J. Crit. Care 44 (2017) 267–272.
[17] S.-F. Sung, C.-Y. Hsieh, Y.-H. Kao Yang, H.-J. Lin, C.-H. Chen, Y.-W. Chen, et al., Developing a stroke severity index based on administrative data was feasible using data mining techniques, J. Clin. Epidemiol. 68 (2015) 1292–1300.
[18] L.-C. Hung, S.-F. Sung, Y.-W. Chen, Validation of a novel claims-based stroke severity index in patients with intracerebral hemorrhage, J. Epidemiol. 27 (2017) 24–29.
[19] S.-F. Sung, Y.-W. Chen, Validity of a stroke severity index for administrative claims data research: a retrospective cohort study, BMC Health Serv. Res. 16 (2016) 509.
[20] S.-F. Sung, Y.-W. Chen, M.-C. Tseng, C.-T. Ong, H.-J. Lin, Atrial fibrillation predicts good functional outcome following intravenous tissue plasminogen activator in patients with severe stroke, Clin. Neurol. Neurosurg. 115 (2013) 892–895.
[21] L. Suissa, D. Bertora, S. Lachaud, M.H. Mahagne, Score for the targeting of atrial fibrillation (STAF): a new approach to the detection of atrial fibrillation in the secondary prevention of ischemic stroke, Stroke 40 (2009) 2866–2868.
[22] C.-Y. Hsieh, C.-H. Lee, D.P. Wu, S.-F. Sung, Prediction of new-onset atrial fibrillation after first-ever ischemic stroke: a comparison of CHADS2, CHA2DS2-VASc and HATCH scores and the added value of stroke severity, Atherosclerosis 272 (2018) 73–79.
[23] J.-M. Bugnicourt, M. Flament, M.-P. Guillaumont, J.-M. Chillon, C. Leclercq, S. Canaple, et al., Predictors of newly diagnosed atrial fibrillation in cryptogenic stroke: a cohort study, Eur. J. Neurol. 20 (2013) 1352–1359.
[24] Y. Li, D. Pastori, Y. Guo, Y. Wang, G.Y.H. Lip, Risk factors for new-onset atrial fibrillation: a focus on Asian populations, Int. J. Cardiol. 261 (2018) 92–98.
[25] L.A. Sposato, P.M. Riccio, V. Hachinski, Poststroke atrial fibrillation: cause or consequence? Critical review of current views, Neurology 82 (2014) 1180–1186.
[26] H.J. Lin, P.A. Wolf, M. Kelly-Hayes, A.S. Beiser, C.S. Kase, E.J. Benjamin, et al., Stroke severity in atrial fibrillation, The Framingham Study, Stroke 27 (1996) 1760–1764.
[27] A.H. Katsanos, P. Korantzopoulos, G. Tsivgoulis, A.P. Kyritsis, M. Kosmidou, S. Giannopoulos, Electrocardiographic abnormalities and cardiac arrhythmias in structural brain lesions, Int. J. Cardiol. 167 (2013) 328–334.
[28] L.A. Sposato, S. Fridman, S.N. Whitehead, R.D. Lopes, Linking stroke-induced heart injury and neurogenic atrial fibrillation: a hypothesis to be proven, J. Electrocardiol. 51 (2018) 430–432.
[29] W.-K. Seo, S.-H. Kang, J.-M. Jung, J.-Y. Choi, K. Oh, Novel composite score to predict atrial Fibrillation in acute stroke patients: AF predicting score in acute stroke, Int. J. Cardiol. 209 (2016) 184–189.
[30] H. Naess, U.W. Andreassen, A score for paroxysmal atrial fibrillation in acute ischemic stroke, Int. J. Stroke 13 (2018) 496–502.
[31] M.A. Baturova, S.H. Sheldon, J. Carlson, P.A. Brady, G. Lin, A.A. Rabinstein, et al., Electrocardiographic and Echocardiographic predictors of paroxysmal atrial fibrillation detected after ischemic stroke, BMC Cardiovasc. Disord. 16 (2016) 209.
[32] L.A. Sposato, R.D. Lopes, Disentangling the risk of atrial fibrillation detected after ischemic stroke (AFDAS): a real challenge in clinical practice, Int. J. Cardiol. 261 (2018) 99–100.
[33] C.-Y. Hsieh, C.-H. Lee, D.P. Wu, S.-F. Sung, Characteristics and outcomes of ischemic stroke in patients with known atrial fibrillation or atrial fibrillation diagnosed after stroke, Int. J. Cardiol. 261 (2018) 68–72.
[34] L.A. Sposato, J.O. Cerasuolo, L.E. Cipriano, J. Fang, S. Fridman, M. Paquet, et al., Atrial fibrillation detected after stroke is related to a low risk of ischemic stroke recurrence, Neurology 90 (2018) e924–e931.
[35] H. Kamel, D.R. Johnson, M. Hegde, A.S. Go, S. Sidney, M. Sorel, et al., Detection of atrial fibrillation after stroke and the risk of recurrent stroke, J. Stroke Cerebrovasc. Dis. 21 (2012) 726–731.
[36] C.-E. Chiang, T.-J. Wu, K.-C. Ueng, T.-F. Chao, K.-C. Chang, C.-C. Wang, et al., 2016 guidelines of the Taiwan heart rhythm society and the Taiwan society of cardiology for the management of atrial fibrillation, J. Formos. Med. Assoc. 115 (2016) 893–952.
[37] J. Aisenberg, P. Kirchhof, F.W.A. Verheugt, R. Veltkamp, Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2, Eur. Heart J. 38 (2017) 860–868.
[38] T. Sanna, H.-C. Diener, R.S. Passman, V. Di Lazzaro, R.A. Bernstein, C.A. Morillo, et al., Cryptogenic stroke and underlying atrial fibrillation, N. Engl. J. Med. 370 (2014) 2478–2486.
[39] D.J. Gladstone, M. Spring, P. Dorian, V. Panzov, K.E. Thorpe, J. Hall, et al., Atrial fibrillation in patients with cryptogenic stroke, N. Engl. J. Med. 370 (2014) 2467–2477.
[40] H. Soejima, H. Ogawa, T. Morimoto, M. Nakayama, S. Okada, M. Sakuma, et al., Aspirin possibly reduces cerebrovascular events in type 2 diabetic patients with higher C-reactive protein level: subanalysis from the JPAD trial, J. Cardiol. 62 (2013) 165–170.