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Monotherapy of acetylsalicylic acid or warfarin for prevention of ischemic stroke in low-risk atrial fibrillation: A Easter Asian population-based study

Chieh-Yu Liu[1, 2], Hui-Chun Chen[3]

[1]Biostatistical Consulting Lab, Department of Speech Language Pathology and Audiology, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan, R.O.C.
[2]Department of Midwifery and Women Health Care, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan, R.O.C.
[3]Department of Nursing, School of Nursing, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan, R.O.C.

Abstract

Background: *This study aimed to investigate the effectiveness of monotherapy acetylsalicylic acid (ASA) and warfarin for stroke prevention in low-risk atrial fibrillation (AF) by using a population-based cohort study in Taiwan.*

Methods: *A newly diagnosed low-risk AF patient cohort were identified by using National Health Insurance Research Database (NHIRD) in Taiwan in 2008. The study cohort was observed with a follow-up of 2 years to examine the onset of ischemic stroke (IS) (to 2010). The longitudinal data were analyzed by using generalized estimation equations (GEE).*

Results: *A total of 8,065 newly-diagnosed low-risk AF patients were identified in 2008. 7.4% were prescribed with ASA and 4.6% were prescribed with warfarin. The GEE results showed that low-risk AF patients with hypertension who received warfarin were associated with a statistically significant 58.4% reduction of IS risk (OR = 0.416, p = 0.024, 95% CI 0.194–0.891). Additionally, low-risk AF patients with hyperlipidemia who received warfarin were associated with a 69.3% reduction of IS risk (OR = 0.307, p = 0.044, 95% CI 0.097–0.969).*

Conclusions: *Warfarin is suggested to be prescribed in preventing IS for low-stroke-risk AF patients with hypertension and hyperlipidemia.* (Cardiol J 2019; 26, 6: 704–710)

Key words: atrial fibrillation, acetylsalicylic acid, warfarin, ischemic stroke, hypertension, diabetes mellitus, hyperlipidemia

Introduction

The prevalence of atrial fibrillation (AF) is increasing in United States, European and Asian countries [1–3]. The incidence of AF was about 1.5 per 1000 person-years in Taiwan [4]. In recent years, although many novel oral anticoagulants (NOACs) were proposed and have been demonstrated significantly effective in stroke prevention, especially in high stroke-risk AF patients, for example, rivaroxaban [5], dabigatran [6] and apixaban [7], but the NOACs were relatively more expensive compared to the two widely-used drugs: warfarin or acetylsalicylic acid (ASA). Consequently, warfarin or ASA were considered to be prescribed for low-stroke-risk AF patients [8]. Although most

Address for correspondence: Professor Chieh-Yu Liu, PhD, 365, Biostatistical Consulting Lab, Department of Speech Language Pathology and Audiology, National Taipei University of Nursing and Health Sciences, Min-der Rd., Beitou district, Taipei City, Taiwan, R.O.C., tel: +886-2-28227101 ext. 3312/6203, fax: +886-2-23891404, e-mail: chiehyu@ntunhs.edu.tw

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published studies aimed mainly to investigate the effectiveness of ASA or warfarin in preventing stroke events for moderate and high-stroke-risk AF patients [9], there remain relatively few studies investigating the effectiveness of preventing stroke events for low-stroke-risk AF patients. One large scale study conducted in the United States found that, among AF patients with high-stroke-risk ($CHADS_2$ score ≥ 2), 38.2% were treated with ASA alone, 61.8% were treated with warfarin or non-vitamin K antagonist oral anticoagulation [9], which indicated that prescribing ASA or warfarin is still very common for high-stroke-risk AF patients. However, prescribing warfarin or ASA to low-stroke-risk AF patients for prevention of stroke is still debatable among clinicians and cardiovascular physicians [10–12], especially for those with metabolic syndromes (including hypertension, diabetes mellitus [DM] and hyperlipidemia) [13]. However, prescribing ASA or warfarin, or combining uses of both drugs to AF patients may be of concern for increasing the risk of unexpected bleeding [14–16], although the incidences of ischemic stroke (IS) is obviously lower for low-risk AF patients. Therefore, investigating the effectiveness of preventing IS of monotherapy of ASA or warfarin in low-stroke-risk AF patients by using a large population-based database is needed [17]. Based on the above mentioned reasons, this study aimed to investigate the effectiveness in preventing IS of monotherapy of ASA or warfarin in low-risk AF patients by using a population-based database, the National Health Insurance Research Database (NHIRD), in Taiwan.

Methods

Study database

This study used claims data from Taiwan's National Health Insurance (NHI) program, which was launched by the Taiwan government in March, 1995 and provided comprehensive health care for 99.5% of its residents in 2010 [18]. The NHIRD contains nationwide information including outpatient, inpatient, dentistry services, prescription drugs, and traditional Chinese medicine services. The diagnostic and procedure codes are based on the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) and Procedure Coding System (ICD-9-PCS).

Ethics statement

The Institutional Review Board of School of Nursing, National Taipei University of Nursing and Health Sciences approved this study (CN-IRB-2011-064). The National Health Research Institutes encrypt the personal information to protect individual information of patients. The National Health Insurance Administration guarantees the confidentiality of the personal and health information of patients.

Study population

An incidence-based patient cohort of newly diagnosed AF patients (ICD-9-CM code 427.31) who had at least two outpatient visits with primary disease of AF and whose CHA_2DS_2-VASc scores were < 2 (= 0 or 1) without a history of stroke events (including IS, hemorrhagic stroke [HS], and transient ischemic attack [TIA]) were identified and retrieved from NHIRD in 2008. This study cohort was followed up for up to 2 years (2010) to observe if they had an IS onset which was also defined by using ICD-9-CM code 430-438 [19]. In order to identify real low-risk AF patients, AF patients with severe baseline diseases were also excluded: cancers, coronary artery disease (CAD, including congenital heart defect [CHD], myocardial infarction [MI], and heart failure [HF]), kidney failure (including chronic kidney failure [CKD]), abnormal renal and liver function as well as peripheral artery disease (PAD). Apart from that, based on one recently published study [11] which showed that combining the use of ASA and warfarin may result in unexpected vascular diseases and some cardiovascular disorders, therefore, patients who used concomitant drugs of both ASA and warfarin were also excluded. The enrollment scheme of study patients is shown in Figure 1.

Covariate assessment

The covariate variables including sex, age, baseline hypertension status, DM status and hyperlipidemia status were also taken into account. Additionally, to identify the low-stroke-risk AF patients, CHA_2DS_2-VASc score was adopted and was defined as: congestive HF, hypertension, age (> 65 = 1 point, > 75 = 2 points), DM, previous stroke or TIA (2 points), vascular disease (including PAD, previous MI, aortic atheroma), and sex (female gender). In this study, the study cohort were all with CHA_2DS_2-VASc score < 2 (0 or 1), which was considered suitable for defining "low-risk" for East Asian AF patients [20, 21]. Besides, the HAS-BLED [22] score was also calculated based on ICD-9-CM code. The HAS-BLED scoring system mainly calculates the risk of major bleeding, which was defined as intracranial bleeding, bleeding requiring hospitalization, a hemoglobin decrease

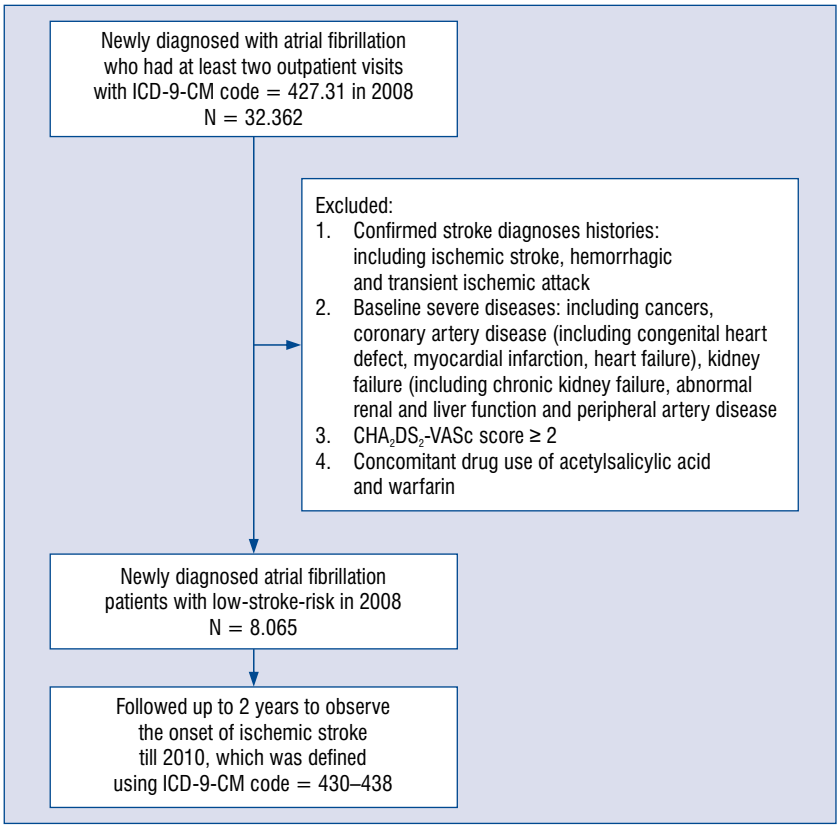

Figure 1. Enrollment scheme of this study.

of more than 2 g/dL, or the need for transfusion secondary to bleeding.

Statistical analysis

The longitudinal data were analyzed by using generalized estimation equations (GEE). GEE is a comprehensive extension of generalized linear models (GLZM) in that they allow for adjusting correlation structure between observations for each subject. The strength of GEE is that they do not require precise specification of multivariate distribution but only of the structure of means or logits for each repeated measurement [23]. In this study, the GEE for longitudinal binary outcome was used (with/without IS) [24]. The modeling was as below:

Define the marginal mean and variances of y_{ij} as $\mu_{ij} = E(\mu_{ij}|X_{ij})$ and $Var(y_{ij}) = \mu_{ij}(1-\mu_{ij})$. Then the marginal logit link function was used:

$$\text{logit}(\mu_{ij}) = \log(\frac{\mu_{ij}}{1-\mu_{ij}}) = \beta' X_{ij}$$

where β is the GEE coefficient vector to be estimated. The GEE estimator $\hat{\beta}$ of β is obtained through estimating the following GEE model:

$$\sum_{i=1}^{n} D'_i V_i^{-1}(y_i - \mu_i) = 0$$

where $\mu_i = (\mu_{i1}, ..., \mu_{ni})'$, $D'_i = \delta\mu_i/\delta\beta$ and V_i is the working covariance matrix of y_i, which can be expressed as $V_i = A_i^{1/2} R_{wi}(\gamma) A_i^{1/2}$, where $R_{wi}(\gamma)$ is a working correlation matrix with parameter γ, which can be estimated from empirical data. In this study, a compound symmetry (or called exchangeable) form of working correlation matrix was used as follows:

$$R_w = \begin{bmatrix} 1 & \rho & \cdots & \rho \\ \rho & 1 & \rho & \rho \\ \vdots & \rho & \ddots & \rho \\ \rho & \cdots & \rho & 1 \end{bmatrix}$$

where ρ was estimated from the data. The odds ratio (OR) of IS of AF patients with and without taking ASA and warfarin were calculated. The results were expressed using ORs with 95% confidence intervals (CIs). My Structured Query Language (MySQL) was used for extraction, linkage, and processing of data. All statistical analyses were performed using IBM SPSS statistical software Version 20 (IBM Corp.,

New York, NY, USA). A two-tailed $p < 0.05$ was considered statistically significant.

Results

This study recruited 8,065 low risk AF patients aged ≥ 20 years old, who had at least two outpatient visits with a primary diagnosis of AF, whose CHA_2DS_2-VASc score < 2 (= 0 or 1), without a history of baseline events of stroke (including HS, IS, and TIA) and without severe baseline diseases which include: cancers, CAD (including CHD, MI, and HF), kidney failure (including CKD) and PAD in 2008. The mean age was 55.95 years old (standard deviation [SD] = 11.60), 78.7% were male and 21.3% were female. Among the study cohort, 4.9% of patients had hypertension, 1.9% with DM, and 2.4% with hyperlipidemia. Additionally, 57.7% of patients were with CHA_2DS_2-VASc score = 0 and 42.3% were with CHA_2DS_2-VASc score = 1. Among the study cohort, 7.4% took ASA and 4.6% took warfarin in 2008 (Table 1).

The distribution of HAS-BLED score was: 89.1% were with 0, 9.5% with 1, and 1.4% with 2. Regarding major bleeding events, according to the database used in this study, there were no major bleeding events found in this study database (Table 1). The incidences of subsequent IS of this study cohort were 2.1% in 2009 and 2.4% in 2010. The results of the GEE model showed that low-risk AF patients who were with hypertension and received warfarin were associated with a statistically significant 58.4% reduction of IS risk (OR = 0.416, p = 0.024, 95% CI 0.194–0.891). Additionally, low-risk AF patients with hyperlipidemia and received warfarin were associated with a statistically significant 69.3% reduction in IS risk (OR = 0.307, p = 0.044, 95% CI 0.097–0.969) (Table 2).

Table 1. Demographic information of study cohort in 2008 (n = 8,065).

	N	%
Age (mean ± SD)	55.95 ± 11.60	
Sex:		
Female	1,719	21.3
Male	6,346	78.7
Hypertension:		
With	396	4.9
Without	7.669	95.1
Diabetes mellitus:		
With	155	1.9
Without	7,910	98.1
Hyperlipidemia:		
With	193	2.4
Without	7,872	97.6
Acetylsalicylic acid:		
Taking	599	7.4
Not taking	7,466	92.6
Warfarin:		
Taking	372	4.6
Not taking	7,693	95.4
CHA_2DS_2-VASc score		
0	4,653	57.7
1	3,412	42.3
HAS-BLED score		
0	7,187	89.1
1	763	9.5
2	115	1.4

SD — standard deviation

Discussion

This study used the Taiwan NHIRD, which is a large-scale population-based database to investigate the effectiveness of preventing IS with a monotherapy of ASA or warfarin among low-stroke-risk AF patients. The results of this study showed that warfarin can help in preventing IS for low-risk AF patients with hypertension and hyperlipidemia. This study agreed with related published studies which defined low-risk solely used CHA_2DS_2-VASc score [25, 26]. Regarding rates of receiving ASA or warfarin, one published study, also using Taiwan NHIRD between 2001 to 2008 showed that the rates of general AF patients (including low-, medium- and high-risk), who received warfarin, ASA, or no treatment in Taiwan was 16%, 62%, and 22% [27]. In comparison with the results of the present study, for low-risk AF patients, 7.4% had a monotherapy of ASA and 4.6% had a monotherapy of warfarin, which were lower than the previously mentioned study [27]. In addition, one published result of a large scale study conducted in the United States [9] in a high-risk group showed that 38.2% of AF patients receiving ASA, and 61.8% receiving warfarin or non-vitamin K antagonist oral anticoagulants.

Regarding the use of ASA for low-risk AF patients, the results of this study did not show a statistically significant effectiveness, which agreed with published studies demonstrating that ASA had limited or non-significant effectiveness for preventing IS in recent years [28, 29]. A randomized clinical trial conducted in Japan showed

Table 2. The results of generalized estimation equations.

Parameter	OR	95% CI for OR		
		Lower	Upper	P
Main effects:				
(Intercept)	0.003	0.002	0.005	< 0.001***
Sex (male vs. female)	0.972	0.687	1.378	0.875
Age	1.010	0.998	1.023	0.106
Year	2.697	2.403	3.027	< 0.001***
ASA	2.377	1.427	3.961	0.001**
WARFARIN	7.345	4.419	12.208	< 0.001***
Hypertension	2.200	1.409	3.436	0.001**
DM	1.760	0.694	4.464	0.234
Hyperlipidemia	3.929	1.516	10.182	0.005**
Interaction effects:				
ASA × Hypertension	1.540	0.737	3.218	0.251
ASA × DM	1.983	0.406	9.693	0.398
ASA × Hyperlipidemia	1.382	0.550	3.469	0.491
WARFARIN × Hypertension	**0.416**	**0.194**	**0.891**	**0.024***
WARFARIN × DM	0.711	0.119	4.238	0.708
WARFARIN × Hyperlipidemia	**0.307**	**0.097**	**0.969**	**0.044***

ASA — acetylsalicylic acid; CI — confidence interval; DM — diabetes mellitus; OR — odds ratio; *p < 0.05; **p < 0.01; ***p < 0.001

that low-dose ASA cannot provide significant effectiveness for stroke prevention among low-risk AF patients [29]. In 2016, the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology issued Guidelines for the management of AF in Taiwan, which stated that ASA did not benefit in stroke prevention in patients with nonvalvular AF, dual antiplatelet therapy (DAPT) of ASA and clopidogrel did not benefit in the prevention of stroke in patients with nonvalvular AF, unless under other therapeutic indications, such as in patients with acute coronary syndrome and receiving stenting therapy [30]. The results of the present study may support the management guideline. Additionally, one expert opinion proposed that ASA may be over-prescribed among AF patients [31], probably due to the low price of ASA compared with warfarin [32]. Therefore, although ASA was widely prescribed, the results of this study showed that ASA did not benefit in preventing IS for low-risk AF patients.

In addition, it is worth noting that low-risk newly diagnosed AF patients still may have a risk of IS onset in the following 2 years (2.1~2.4% as shown in the present study), which was similar with one large scale study conducted in European countries which showed that IS incidence rates were 2.1, 3.0, and 4.2% for paroxysmal, persistent, and permanent AF, respectively [33]. In summary, results of this study can provide some clinical implications: first, intensive monitoring of stroke events (including HS, IS and TIA), which is strongly suggested and some associated symptoms, for example, FAST [34]: face drooping, arm weakness, speech difficulty and time to call emergency help (ex. 911) and low-risk AF patients should be carefully reminded of this. Second, warfarin can help in preventing IS for low-risk AF patients with hypertension and hyperlipidemia.

Limitations of the study

This study had some limitations. First, the NHIRD did not provide information of potential confounders including smoking, alcohol drinking, life style, diet and other factors, which are associated with the risk of IS. Second, AF patients can buy over-the-counter ASA in drug stores, which were not recorded in NHIRD, so that some AF patients may use warfarin concurrently with ASA, which will result in an underestimate for the number of patients using ASA. One published study proposed that combining the use of ASA and warfarin was inappropriate [11], it is believed that a number of AF patients may concurrently use both

ASA and warfarin, which could not be identified in NHIRD. Third, due to the nature of the study database, it was an outpatient claims database which provided only drug prescriptions without dosage information, therefore the dose effect could not be analyzed and was regarded as another study limitation. Fourth, published studies have shown that poor adherence to anticoagulation guidelines in patients with AF [35–37]. Although we may code one AF patient with the prescription of ASA or warfarin from the claims database, it could not be verified that the information of drug compliance of the recruited AF patients in this study was carried out. Lastly, although there were no major bleeding events found in this study database, there were probably minor bleeding events which were not recorded in NHIRD, which was also regarded as a study limitation.

Conclusions

The present study used a large scale population-based database which showed that monotherapy of warfarin was suggested in prescribing for the prevention of IS in low-stroke-risk AF patients, especially for low-risk AF patients with hypertension and hyperlipidemia.

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Conflict of interest: None declared

References

1. Lee SR, Choi EK, Han KD, et al. Trends in the incidence and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHADS-VASc score in the entire Korean population. Int J Cardiol. 2017; 236: 226–231, doi: 10.1016/j.ijcard.2017.02.039, indexed in Pubmed: 28233629.
2. Schnabel RB, Johannsen SS, Wild PS, et al. [Prevalence and risk factors of atrial fibrillation in Germany : data from the Gutenberg Health Study]. Herz. 2015; 40(1): 8–15, doi: 10.1007/s00059-014-4199-6, indexed in Pubmed: 25604071.
3. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. J Intern Med. 2013; 274(5): 461–468, doi: 10.1111/joim.12114, indexed in Pubmed: 23879838.
4. Chao TF, Chiang CE, Chen SA. Stroke in atrial fibrillation: long-term follow-up of cardiovascular events. Arrhythm Electrophysiol Rev. 2013; 2(2): 105–108, doi: 10.15420/aer.2013.2.2.105, indexed in Pubmed: 26835049.
5. Perzborn E, Kubitza D, Misselwitz F. Rivaroxaban. A novel, oral, direct factor Xa inhibitor in clinical development for the prevention and treatment of thromboembolic disorders. Hamostaseologie. 2007; 27(4): 282–289, indexed in Pubmed: 17938768.
6. Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361(12): 1139–1151, doi: 10.1056/NEJMoa0905561, indexed in Pubmed: 19717844.
7. Eikelboom JW, O'Donnell M, Yusuf S, et al. Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. Am Heart J. 2010; 159(3): 348–353.e1, doi: 10.1016/j.ahj.2009.08.026, indexed in Pubmed: 20211294.
8. Miller VT, Rothrock JF, Pearce LA, et al. Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. Stroke Prevention in Atrial Fibrillation Investigators. Neurology. 1993; 43(1): 32–36, indexed in Pubmed: 8423907.
9. Hsu JC, Maddox TM, Kennedy K, et al. Aspirin Instead of Oral Anticoagulant Prescription in Atrial Fibrillation Patients at Risk for Stroke. J Am Coll Cardiol. 2016; 67(25): 2913–2923, doi: 10.1016/j.jacc.2016.03.581, indexed in Pubmed: 27339487.
10. Poulsen MB, Binici Z, Dominguez H, et al. Performance of short ECG recordings twice daily to detect paroxysmal atrial fibrillation in stroke and transient ischemic attack patients. Int J Stroke. 2017; 12(2): 192–196, doi: 10.1177/1747493016669883, indexed in Pubmed: 27694312.
11. Turan B, Demir H, Mutlu A, et al. Inappropriate combination of warfarin and aspirin. Anatol J Cardiol. 2016; 16(3): 189–196, doi: 10.5152/akd.2015.6050, indexed in Pubmed: 26467380.
12. Schrör K. Why we should not skip aspirin in cardiovascular prevention. Hamostaseologie. 2016; 36(1): 33–43, doi: 10.5482/hamo-14-10-0048, indexed in Pubmed: 25891122.
13. Stroke Prevention in Atrial Fibrillation I. A differential effect of aspirin on prevention of stroke in atrial fibrillation. J Stroke Cerebrovasc Dis. 1993; 3(3): 181–188, doi: 10.1016/s1052-3057(10)80159-4.
14. Gieling EM, van den Ham HA, van Onzenoort H, et al. Risk of major bleeding and stroke associated with the use of vitamin K antagonists, nonvitamin K antagonist oral anticoagulants and aspirin in patients with atrial fibrillation: a cohort study. Br J Clin Pharmacol. 2017; 83(8): 1844–1859, doi: 10.1111/bcp.13265, indexed in Pubmed: 28205318.
15. Vazquez FJ, Gonzalez JP, LeGal G, et al. Risk of major bleeding in patients receiving vitamin K antagonists or low doses of aspirin. A systematic review and meta-analysis. Thromb Res. 2016; 138: 1–6, doi: 10.1016/j.thromres.2015.12.013, indexed in Pubmed: 26826501.
16. Shah R, Hellkamp A, Lokhnygina Y, et al. ROCKET AF Steering Committee Investigators. Use of concomitant aspirin in patients with atrial fibrillation: Findings from the ROCKET AF trial. Am Heart J. 2016; 179: 77–86, doi: 10.1016/j.ahj.2016.05.019, indexed in Pubmed: 27595682.
17. Yang YJ, Yuan JQ, Fan CM, et al. Incidence of ischemic stroke and systemic embolism in patients with hypertrophic cardiomyopathy, nonvalvular atrial fibrillation, CHA2DS2-VASc score of ≤1 and without anticoagulant therapy. Heart Vessels. 2016; 31(7): 1148–1153, doi: 10.1007/s00380-015-0718-5, indexed in Pubmed: 26231425.

18. Yeh MJ, Chang HH. National Health Insurance In Taiwan. Health Aff (Millwood). 2015; 34(6): 1067, doi: 10.1377/hlthaff.2015.0447, indexed in Pubmed: 26056216.
19. Lee CC, Tsai KY, Hung YT, et al. Association of hypnotics with stroke risk: a population-based case-control study. Prim Care Companion CNS Disord. 2014; 16(2), doi: 10.4088/PCC.13m01583, indexed in Pubmed: 25133061.
20. Pieri A, Lopes TO, Gabbai AA. Stratification with CHA2DS2-VASc score is better than CHADS2 score in reducing ischemic stroke risk in patients with atrial fibrillation. Int J Stroke. 2011; 6(5): 466, doi: 10.1111/j.1747-4949.2011.00650.x, indexed in Pubmed: 21951414.
21. Xiong Q, Chen S, Senoo K, et al. The CHADS2 and CHA2DS2-VASc scores for predicting ischemic stroke among East Asian patients with atrial fibrillation: A systemic review and meta-analysis. Int J Cardiol. 2015; 195: 237–242, doi: 10.1016/j.ijcard.2015.05.115, indexed in Pubmed: 26048384.
22. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010; 138(5): 1093–1100, doi: 10.1378/chest.10-0134, indexed in Pubmed: 20299623.
23. Liang KY, Zeger S. Longitudinal data analysis using generalized linear models. Biometrika. 1986; 73(1): 13–22, doi: 10.1093/biomet/73.1.13.
24. Lipsitz S, Laird N, Harrington D. Generalized estimating equations for correlated binary data: Using the odds ratio as a measure of association. Biometrika. 1991; 78(1): 153–160, doi: 10.1093/biomet/78.1.153.
25. Turagam MK, Velagapudi P, Leal MA, et al. Aspirin in stroke prevention in nonvalvular atrial fibrillation and stable vascular disease: an era of new anticoagulants. Expert Rev Cardiovasc Ther. 2012; 10(4): 433–439, doi: 10.1586/erc.12.19, indexed in Pubmed: 22458577.
26. Wändell P, Carlsson A, Holzmann M, et al. Warfarin treatment and risk of stroke among primary care patients with atrial fibrillation. Scand Cardiovasc J. 2016; 50(5-6): 311–316, doi: 10.1080/14017431.2016.1215519.
27. Chang CH, Yang YHK, Chen JH, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation in Taiwan. Thromb Res. 2014; 133(5): 782–789, doi: 10.1016/j.thromres.2014.02.024, indexed in Pubmed: 24642004.
28. Lip GYH, Lane DA, Lip GYH. The role of aspirin for stroke prevention in atrial fibrillation. Nat Rev Cardiol. 2011; 8(10): 602–606, doi: 10.1038/nrcardio.2011.112, indexed in Pubmed: 21788962.
29. Sato H, Ishikawa K, Kitabatake A, et al. Japan Atrial Fibrillation Stroke Trial Group. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial. Stroke. 2006; 37(2): 447–451, doi: 10.1161/01.STR.0000198839.61112.ee, indexed in Pubmed: 16385088.
30. Chiang CE, Wu TJ, Ueng KC, 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. 2016; 115(11): 893–952, doi: 10.1016/j.jfma.2016.10.005, indexed in Pubmed: 27890386.
31. Taylor J. Aspirin still overprescribed for stroke prevention in atrial fibrillation. Eur Heart J. 2014; 35(22): 1422, indexed in Pubmed: 25035872.
32. Sterne JAc, Bodalia PN, Bryden PA, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess. 2017; 21(9): 1–386, doi: 10.3310/hta21090, indexed in Pubmed: 28279251.
33. Vanassche T, Lauw MN, Eikelboom JW, et al. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. Eur Heart J. 2015; 36(5): 281–7a, doi: 10.1093/eurheartj/ehu307, indexed in Pubmed: 25187524.
34. Jin J. JAMA patient page. Warning signs of a stroke. JAMA. 2014; 311(16): 1704, doi: 10.1001/jama.2014.2296, indexed in Pubmed: 24756530.
35. Kew GS, Tan M, Lim TW. Poor adherence to anticoagulation guidelines in patients with non-valvular atrial fibrillation treated in a tertiary cardiology unit. Heart Asia. 2015; 7(1): 18–22, doi: 10.1136/heartasia-2014-010600, indexed in Pubmed: 27326208.
36. Račkauskas G, Zabiela V, Marinskis G, et al. Evaluation of atrial fibrillation management and cardiovascular risk profile in atrial fibrillation patients: A cross-sectional survey. Medicina (Kaunas). 2017; 53(1): 19–25, doi: 10.1016/j.medici.2017.01.005, indexed in Pubmed: 28284524.
37. Vallakati A, Lewis WR. Underuse of anticoagulation in patients with atrial fibrillation. Postgrad Med. 2016; 128(2): 191–200, doi: 10.1080/00325481.2016.1132939, indexed in Pubmed: 26666288.