Available online at www.sciencedirect.com

ScienceDirect

Chronic Diseases and Translational Medicine 1 (2015) 203–209

www.keaipublishing.com/en/journals/cdtm/

www.cdatm.org

Original article

Does novel oral anticoagulant improve anticoagulation for non-valvular atrial fibrillation associated stroke: An inpatient registration study in Shanghai

Feng-Di Liu [1], Rong Zhao [1], Xue-Mei Wang, Shuo Wang, Xiao-Lei Shen, Xiao-Xiao Tao, Bo Zheng, Jia-Li Peng, Hui Zhang, Ran Mo, Yan Tong, Wen-Ting Li, Xiao-Yan Feng, Ge-Fei Li, Liang Shu **, Jian-Ren Liu*

Department of Neurology and Jiuyuan Municipal Stroke Center, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China

Received 8 September 2015
Available online 8 January 2016

Abstracts

Objective: To summarize the use rate, safety, efficacy of antithrombotics in stroke/transient ischemic attack (TIA) prevention, and reasons for not using dabigatran etexilate (DE) in Shanghai, China.

Methods: Non-valvular atrial fibrillation (NVAF)-associated stroke patients were prospectively registered as an electronic database. Use rate of antithrombotics and reasons for not using DE were extracted during follow-up. Patients' baseline characteristics, recurrent ischemic stroke/TIA events and bleeding complications were analyzed.

Patients: From April 2012 to August 2014, 110 inpatients with NVAF-associated stroke were studied in our hospital. NVAF was diagnosed by 12-lead electrocardiogram, 24 h Holter and echocardiography.

Results: Before introduction of DE (April 2013), use rates of warfarin and antiplatelets were 28.9% (11/38) and 60.5% (23/38) respectively; after that, use rates of warfarin, DE, and antiplatelets were 20.8% (15/72), 12.5% (9/72), and 43.1% (31/72). The DE did not improve use of anticoagulants ($P = 0.639$). There were 19 (17.3%) recurrent ischemic stroke events up to October 2015; two (9.5%) in the non-user group, 10 (18.5%) in the antiplatelet group, and seven (20.0%) in the anticoagulants group ($P = 0.570$). Furthermore, recurrence rates were similar between the DE group (20.0%) and the Warfarin group (20.0%, $P = 1.000$). The most common reason for not using DE was financial concerns (61.0%), followed by inconvenience to purchase (14.0%) and hemorrhage concerns (11.0%). Two patients using warfarin found fecal occult blood so they stopped warfarin and began to use antiplatelet drugs. No bleeding event occurred in the other groups. Only one patient had side effects (dyspepsia and gastroesophageal reflux) from DE.

* Corresponding author. 639 Zhizaoju Road, Huangpu District, Shanghai, China, 200011. Tel.: +86 21 6308 1475.
** Corresponding author. 639 Zhizaoju Road, Huangpu District, Shanghai, China, 200011. Tel.: +86 21 6308 1475.
E-mail addresses: shuliang_9@hotmail.com (L. Shu), liujr021_201410@126.com (J.-R. Liu).
Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

[1] The two authors contributed equally.

http://dx.doi.org/10.1016/j.cdtm.2015.11.005

Conclusion: The use rate of either DE or warfarin in Shanghai was low; DE had not improved anticoagulation therapy for NVAF patients in Shanghai mainly because DE had not been covered by health insurance.

Keywords: Dabigatran etexilate; Novel oral anticoagulant; Cardiogenic cerebral embolism; Non-valvular atrial fibrillation; Real-world study

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice.[1,2] It has been estimated that by 2050 there will be 72 million AF patients in Asia,[3] more than double the combined number of patients from Europe and the United States.[4,5] There are almost 8 million patients with AF in China[6] and they have a 5-fold higher risk of ischemic stroke. Over 20% of all strokes can be attributed to AF and the mortality rate is two times higher than that without AF.[7] Embolic cerebral infarction associated with AF can be prevented by oral anticoagulants.[8] Non-valvular atrial fibrillation (NVAF) is a type of AF that does not associate with rheumatic heart disease, artificial valve replacement, and valve repair. The thromboembolism rate per 100 patient-years with NVAF was 4.8 in Danmark[9] and 4.2 in the Middle East.[10] According to recent guidelines, NVAF patients with stroke risk should receive Warfarin or novel oral anticoagulants therapy (NOACs).[11,12]

The use rate of warfarin before introduction of NOACs was 66.8% in America,[13] 65.2% in Australia, 63.9% in Europe, 39.7% in the Asia−Pacific region, 37.2% in Latin America, 25.1% in Taiwan, China,[14] and 16.2%−20.3% in the mainland of China.[15,16] The low use rate of warfarin in China could be partly explained by the limitation of warfarin; for example, a long half-life period, a slow onset, a high plasma protein binding rate, different metabolism rate among individuals, drug−drug interactions and drug−food interactions, and dosing frequency. Now that there are four kinds of NOACs and many clinical trials, like RE-LY,[17] ROCKET-AF,[18] ARISTOTLE[19] and ENGAGE AF-TIMI 48,[20] that have all shown no inferiority and a low bleeding rate, could they improve anticoagulation for NVAF-associated stroke patients in China?

Dabigatran etexilate (DE) is the only kind of NOAC that has been approved by the Chinese Food and Drug Administration (April 2013). Since the use rate of warfarin and the rate of INRs in the therapeutic range of 2.0−3.0 were low in the Mainland of China,[16] DE has the possibility of overcoming the shortcomings of warfarin. It has been three years since DE was introduced into the Chinese market; however, the use rate of DE in Shanghai and its efficacy have not been reported yet.

This study recruited 110 patients with NVAF-associated cerebral embolism in our stroke center from April 2012 to August 2014 to investigate use of antithrombotics and the influence of DE in anticoagulation therapy for NVAF patients.

Methods

Patients

From April 2012 to August 2014, 110 inpatients with AF associated cardiogenic cerebral embolism were prospectively registered in an electronic database in our stroke center. AF was diagnosed by 12-lead electrocardiogram or 24 h Holter and valvular AF was excluded by echocardiography. The study has obtained the consent of the ethics committee of our hospital and all patients or their relatives signed consent to participate in this prospective registration study. The patients' treatment was decided by neurologists in our hospital. After their discharge, their follow-ups were done both in our hospital and in community hospitals.

Study design

This was a single-center, registry-based study. Patients' data included gender, age, medical conditions, prior medications, the results of clinical examinations, and medications when they were discharged. We conducted telephone follow-up from October 12th to October 19th 2015. Questions included recurrent ischemic stroke events, current anticoagulants or antiplatelet drugs, reasons for not using DE, current INR if using warfarin, and complications (bleeding). To patients enrolled before March 31st, 2013, their previous medications were also questioned. We analyzed patients' baseline characteristics, recurrent ischemic

stroke or transient ischemic attack (TIA) events, use rate of antithrombotics before and after introduction of DE, bleeding complications, current INR if using warfarin, and reasons for not using DE.

Statistical analysis

Categorical variables were reported as number or percentage; continuous variables fitting a normal distribution were expressed as mean ± standard deviation (SD). Statistical comparisons of the baseline characteristics were performed using a Chi-square test, analysis of variance (ANOVA), Student's *t* test or Fisher's exact test as appropriate. Variables with a *P* value <0.05 was considered statistically significant. Data analysis was performed using IBM SPSS Statistics 19 (SPSS, Inc., Chicago, Illinois, USA).

Results

Baseline characteristics

A total of 110 patients were included in the final analysis. The mean age was 77.8 ± 9.8 years with a female predominance (61.8%). The mean CHA2DS2-Vasc score was 5.3 ± 1.3 and the mean HAS-BLED score was 3.1 ± 0.9. Of all the 110 patients, 85 (77.3%) had persistent AF, 76 (69.1%) patients had hypertension and 41 (37.3%) had diabetes mellitus. More patients without antithrombotics had hypertension (90.5%, $P = 0.046$) (Table 1).

Use rate of anticoagulants and antiplatelet drugs

Over a mean follow-up period of 23.0 ± 8.4 months there was a drop-out rate of 6.0%, the use rate of DE was 9.1% (20% for 150 mg b.i.d. and 80% for 110 mg b.i.d.), warfarin was 22.7% and antiplatelet agents was 49.1%. The mean INR of the warfarin group was 2.2 ± 0.3. In the antiplatelet agents group, the use rate of Aspirin 100 mg q.d. was 28.2%, clopidogrel 75 mg q.d. was 8.2%, Aspirin plus clopidogrel was 0.9%, and Tab Cilostazol 100 mg b.i.d. (for those having hemorrhagic transformation) was 11.8% (Fig. 1). Before introduction of DE, the use rate of warfarin was 28.9% (11/38). After the introduction of DE from April 2013, use rates of warfarin and DE were 20.8% (15/72) and 12.5% (9/72) respectively. DE did not improve use of anticoagulants ($P = 0.639$) (Table 2).

Reasons for not using DE

Among those who did not receive DE, financial concerns ranked first with 61.0%, followed by inconvenience of purchase (14.0%) and hemorrhage concerns (11.0%). Six patients (6.0%) had severe renal disease (creatinine clearance (CrCl) <30 ml/min) which was contraindication for DE. Two patients (2.0%) died during follow-up and drop-out rate was 6.0% (Fig. 2).

Complications

Of all the 10 patients using DE, only one patient had dyspepsia and gastroesophageal reflux. Two patients using warfarin found fecal occult blood so they stopped warfarin and began to use antiplatelet drugs. No bleeding event occurred in other groups.

Recurrent ischemic stroke events

Up to October 2015, there were 19 recurrent ischemic stroke events. Recurrence rates of the three

Table 1
Baseline characteristics of all the 110 patients.

	Without antithrombotics ($n = 21$)	With anticoagulants ($n = 35$)	With antiplatelet drugs ($n = 54$)	*P*-value
Female, %	15 (71.4)	22 (62.9)	31 (57.4)	0.527
Age, years	78.0 ± 9.8	77.2 ± 9.5	78.2 ± 10.6	0.904
Persistent AF, %	19 (90.0)	29 (82.9)	38 (70.4)	0.120
Hypertension, %	19 (90.5)	21 (60.0)	35 (64.8)	0.046*
Diabetes mellitus, %	10 (47.6)	12 (34.3)	20 (37.0)	0.592
Severe renal disease, %	1 (4.8)	1 (2.9)	4 (7.4)	0.645
Abnormal hepatic function, %	7 (33.3)	7 (20.0)	10 (18.5)	0.632
NIHSS on admission	7.9 ± 6.9	6.3 ± 6.6	6.1 ± 5.4	0.523
CHA2DS2-Vasc	5.7 ± 1.0	5.1 ± 1.4	5.2 ± 1.3	0.172
HAS-BLED	3.4 ± 0.9	2.9 ± 0.9	3.2 ± 1.0	0.098

AF:atrial fibrillation; DE:dabigatran etexilate; Values are mean ± SD or *n* (%). Baseline defined as date of atrial fibrillation. Data were from April 1, 2012 to August 31, 2014. Severe renal disease defined as CrCl <30 ml/min.

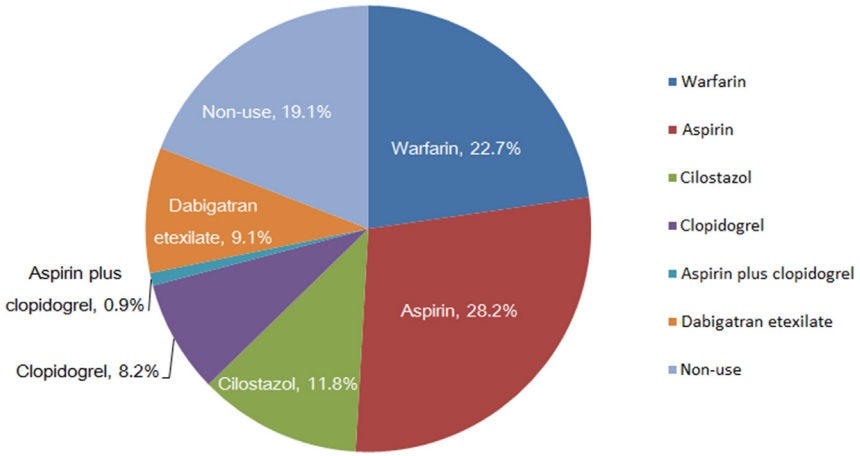

Fig. 1. Use rates of anticoagulants and antiplatelet drugs in patients with non-valvular atrial fibrillation associated stroke in 2015. Tab Aspirin 100 mg q.d.; Tab clopidogrel 75 mg q.d.; Tab Cilostazol 100 mg b.i.d.; Tab Dabigatran etexilate 110 mg (80%) or 150 mg (20%) b.i.d.; for warfarin group, the mean INR is 2.2 ± 0.3.

Table 2
Use rate of antithrombotics and baseline characteristics comparison before and after introduction of DE.

Indices	Before March 31st, 2013 (n = 38)	After April 1st, 2013 (n = 72)	P-value
Female, %	23(60.5)	45(62.5)	0.839
Age, years	78.2 ± 11.6	77.6 ± 8.8	0.077
Persistent AF, %	27(71.1)	59(81.9)	0.188
Hypertension, %	28(73.7)	47(65.3)	0.368
Diabetes mellitus, %	18(47.4)	24(33.3)	0.150
Severe renal disease, %	2(5.3)	4(5.6)	1.000
Abnormal hepatic function, %	12(31.6)	12(16.7)	0.088
NIHSS on admission	6.3 ± 5.7	6.6 ± 6.3	0.835
CHA2DS2-Vasc	5.4 ± 1.2	5.3 ± 1.3	0.571
HAS-BLED	3.2 ± 0.9	3.1 ± 0.9	0.589
With anticoagulants, %	11 (28.9)	24 (33.3)	0.639
Without antithrombotics, %	4 (10.5)	17 (23.6)	0.097

AF:atrial fibrillation; DE dabigatran etexilate.

groups were 20.0% (seven patients) for anticoagulants, 18.5% (ten patients) for antiplatelet drugs and 9.5% (two patients) for non-users (P = 0.570). Furthermore, recurrence rates were similar between the DE group (20.0%) and the Warfarin group (20.0%, P = 1.000). No TIA occurred in any group.

Discussion

The use rate of warfarin in our stroke center was 22.7%, a little higher than that reported before (16.3%–20.3%).[15,16] However, compared with the use rate (63.9%) in European countries, ours was far lower. Chiang and his group[21] compared Asians and non-Asians from the RE-LY trial, the ROCKET AF trial and the ARISTOTLE trial and pointed out that warfarin was 'difficult' to use in Asians due to a higher risk of bleeding, unstable INR and higher stroke rate. However, excessive bleeding was not found in Asians when NOACs were used, besides, the superiority of NOACs to warfarin in reducing thromboembolism was maintained; therefore NOACs are preferentially indicated in Asians in terms of both efficacy and safety.

The use rate of DE was only 9.1% in our center. In Europe, DE was the most frequently used alternative option to warfarin and the ratio of warfarin and NOACs was 1/1.5.[22] According to our results, the ratio of warfarin and NOACs was 2.5/1 in our center. Although use rate of warfarin decreased after introduction of DE, DE did not improve anticoagulation therapy for NVAF patients (28.9% before introduction and 33.3% after introduction, P = 0.639). Since DE was highly anticipated to take the place of Warfarin, why was the use rate of DE still low in Shanghai?

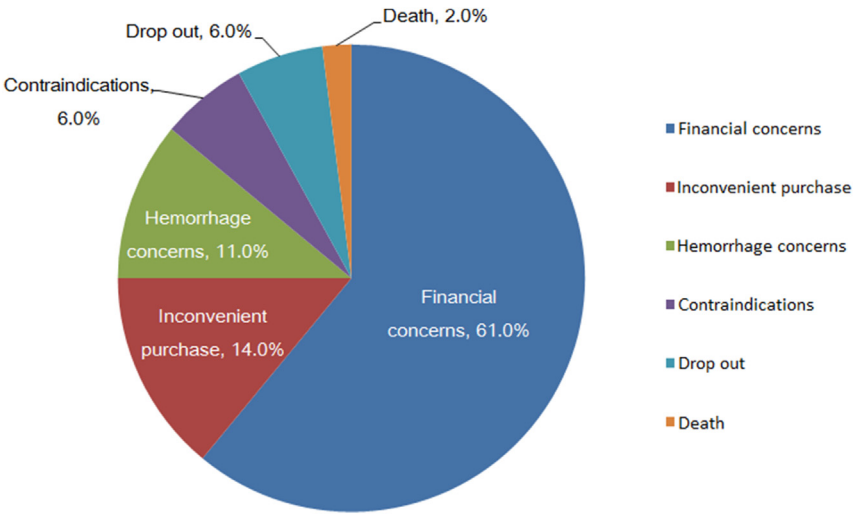

Fig. 2. Reasons for not using Dabigatran etexilate in patients with non-valvular atrial fibrillation associated stroke in 2015. Follow-up time is 23.0 ± 8.4 months (mean ± SD), and drop-out rate is 6.0%.

Financial concerns were the main reason because DE had not been covered by the health insurance in Mainland of China. There are two dosages of DE, 150 mg for 25.1 Chinese yuan per pill and 110 mg for 19.8 Chinese yuan per pill, so a total of 50 Chinese yuan per day will be the cost if a patient takes the recommended dosage (150 mg b.i.d.), while only 0.5 Chinese yuan per day will cost if he chooses warfarin. Most (80%) patients in our report who received anticoagulation therapy took DE 110 mg b.i.d. for economy and safety.

The other reason was inconvenience of purchase. DE was introduced into the Chinese mainland market in March 2013, and at the beginning only one pharmacy in Shanghai provided DE. Moreover it also required an appointment for registration. It takes about one week from book to get the drugs. The majority of drugs in mainland of China are not associated with this kind of inconvenience. The problem may be that DE is a new and expensive drug without the support of medicare.

Severe renal insufficiency was the contraindication of DE, and six patients in our study did not receive DE because their CrCl was less than 30 ml/min. Instead, they were recommended for warfarin (one patient) or antiplatelet therapy (five patients). In addition, prescription instructions pointed out that "clinical trials of AF related stroke excluded patients with elevated liver enzymes >2ULN (the upper limit of normal), so for this subgroup, treatment experience is lacking and the use of this product is not recommend".[23] Therefore in our clinical practice, we recommend liver-protection treatment when the patients' liver enzymes were higher than 2ULN. One patient in our study received liver protection treatment before use of DE and was normal after discharge. Now he has taken DE for 25 months and his liver function has remained normal.

The most common side effect of DE was dyspepsia (13.2%/ year), followed by minor bleeding like skin rash and pruritus (11.5%/ year). Other side effects included gastroesophageal reflux, headache and generalized discomfort (5.5%/ year).[16] In our study, there were no reported complications except for one patient having dyspepsia and gastroesophageal reflux. Reported bleeding events include a 4.1% per year incidence of major gastrointestinal bleeding, intracranial hemorrhage 0.5% per year and myocardial infarction of 0.5% per year in Hong Kong, China.[24] One prospective cohort study in Denmark showed that less intracranial bleeding was seen with both DE doses and gastrointestinal bleeding was lower with DE at 110 mg b.i.d. compared with warfarin.[25] So 80% of patients received DE at 110 mg b.i.d. since their average age was 80.6 ± 7.5 years, HAS-BLED score was 2.9 ± 0.7 and DE was not covered by medicare. No bleeding event occurred in DE patients according to our study. Shanghai had a large aging population, and the incidence of AF was higher with aging and frequent INR detection was not ideal for most cases. If DE is covered by medicare, low dose DE would be used extensively because of its safety, convenience, and efficacy and improved anticoagulation therapy for NVAF.

Research has shown that aspirin alone had a weak effect on stroke prevention in AF patients[26–28] and patients with cardioembolic stroke, who were unwilling or unable to take oral anticoagulants, had the greatest risk of stroke recurrence.[29] According to our study, 19 patients underwent recurrent stroke (17.3%). Recurrence rates of the three groups were 20.0% for anticoagulants, 18.5% for antiplatelet drugs and 9.5% for non-users ($P = 0.570$) respectively. No superiority was found between anticoagulant groups and other groups; this could be because in our study, the number of patients was relatively few.

In patients with NVAF and an increased risk of stroke, prophylaxis, apixaban, dabigatran, and rivaroxaban are all cost-effective alternatives to warfarin.[30,31] Therefore, it is necessary to list DE into Chinese medicare, thus enabling more patients to use DE to prevent NVAF-associated stroke.

Conclusions

The use rate of anticoagulants was low (DE 9.1%, Warfarin 22.7%) in NVAF-associated stroke in real world practice according to our study; DE did not significantly improve anticoagulation therapy for NVAF patients in our center mainly because DE had not been covered by Chinese medicare.

Sources of funding

This work was supported by the “prevention and control of chronic diseases project” of Shanghai Hospital Development Center [No. SHDC12015310, to J.R. Liu], early development program from Clinical Research Center of Brain Disease [No. 2015NKX006, to J.R. Liu], the National Natural Science Foundation of China [No. 81271302 to J.R. Liu], the “Science and Technology Project” of the Shanghai Pudong New Area Health Bureau (Pudong New Area Population and Family Planning Commission) [No. PW 2013D-4, to J.R. Liu], research innovation project from Shanghai Municipal Science and Technology Commission [No. 14JC1404300, to J.R. Liu], and State Key Laboratory of Medical Neurobiology, Fudan University [No. SKLMN2014002 to J.R. Liu].

References

1. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Europace*. 2010;12:1360–1420.
2. Lip GY, Tse HF, Lane DA. Atrial fibrillation. *Lancet*. 2012;2012(379):648–661.
3. Tse HF, Wang YJ, Ahmed Ai-Abdullah M, et al. Stroke prevention in atrial fibrillation-an Asian stroke perspective. *Heart Rhythm*. 2013;10:1082–1088.
4. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125.
5. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34:2746–2751.
6. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol*. 2014;11:639–654.
7. Li SY, Zhao XQ, Wang CX, et al. One-year clinical prediction in Chinese ischemic stroke patients using the CHADS2 and CHA2DS2-VASc scores: the China National Stroke Registry. *CNS Neurosci Ther*. 2012;18:988–993.
8. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev*. 2005;3. CD001927.
9. Ahlehoff O, Gislason G, Lamberts M, et al. Risk of thromboembolism and fatal stroke in patients with psoriasis and non-valvular atrial fibrillation: a Danish nationwide cohort study. *J Intern Med*. 2015;277:447–455.
10. Zubaid M, Rashed WA, Alsheikh-Ali AA, et al. Management and 1-year outcomes of patients with atrial fibrillation in the Middle East: gulf survey of atrial fibrillation events. *Angiology*. 2015;66:464–471.
11. Camm AJ. 2012 Focused update of the ESC guidelines for the management of atrial fibrillation. *Europace*. 2012;14:1385–1413.
12. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American college of cardiology/American heart association task force on practice guidelines and the heart rhythm society. *Circulation*. 2014;130:2071–2104.
13. Raji MA, Lowery M, Lin YL, Kuo YF, Baillargeon J, Goodwin JS. National utilization patterns of warfarin use in older patients with atrial fibrillation: a population-based study of medicare part D beneficiaries. *Ann Pharmacother*. 2013;47:35–42.
14. Suarez J, Piccini JP, Liang L, et al. International variation in use of oral anticoagulation among heart failure patients with atrial fibrillation. *Am Heart J*. 2012;163:804–811.
15. Huisman MV, Rothman KJ, Paquette M, et al. Antithrombotic treatment patterns in 10 871 patients with newly diagnosed non-valvular atrial fibrillation: the GLORIA-AF Registry Program, Phase II. *Am J Med*. 2015 Jul 31. http://dx.doi.org/10.1016/j.amjmed.2015.07.013. pii: S0002–9343(15)00687-7 [Epub ahead of print].
16. Wang C, Yang Z, Wang C, et al. Significant underuse of warfarin in patients with nonvalvular atrial fibrillation: results from the china national stroke registry. *J Stroke Cerebrovasc Dis*. 2014;23:1157–1163.
17. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
18. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.

19. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981−992.
20. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093−2104.
21. Chiang CE, Wang KL, Lip GY. Stroke prevention in atrial fibrillation: an Asian perspective. *Thromb Haemost*. 2014;111:789−797.
22. Olesen JB, Sørensen R, Hansen ML, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011−2013. *Europace*. 2015;17:187−193.
23. Karly P, Garnock-Jones. Dabigatran etexilate. *Am J Cardiovasc Drugs*. 2011;11:57−72.
24. Ho MH, Ho CW, Cheung E, et al. Continuation of dabigatran therapy in "real-world" practice in Hong Kong. *PLoS One*. 2014;9:e101245.
25. Larsen TB, Rasmussen LH, Skjøth F, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol*. 2013;61:2264−2273.
26. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007;370:493−503.
27. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have non-valvular atrial fibrillation. *Ann Intern Med*. 2007;146:857−867.
28. Flaker GC, Eikelboom JW, Shestakovska O, et al. Bleeding during treatment with aspirin versus apixaban in patients with atrial fibrillation unsuitable for warfarin: the apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial. *Stroke*. 2012;43:3291−3297.
29. Toni D, Di Angelantonio E, Di Mascio MT, Vinisko R, Bath PM, PRoFESS Study Group. Types of stroke recurrence in patients with ischemic stroke: a substudy from the PRoFESS trial. *Int J Stroke*. 2014;9:873−878.
30. Harrington AR, Armstrong EP, Nolan Jr PE, Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. *Stroke*. 2013;44:1676−1681.
31. Amin A, Stokes M, Makenbaeva D, Wiederkehr D, Wu N, Lawrence JH. Estimated medical cost reductions associated with use of novel oral anticoagulants vs. warfarin in a real-world non-valvular atrial fibrillation patient population. *J Med Econ*. 2014;17:771−781.

Edited by Wei-Zhu Liu