Original Research Article

Rivaroxaban versus warfarin in Chinese elder diabetic patients with non-valvular atrial fibrillation: A retrospective study on the effectiveness and associated risks (EAR) analysis

Shangcai Wang*, Rui Qiang, Heng Zhang
Department of General Medicine, Huilongguan Community Health Service Center, Beijing, 100096, China

For correspondence: **Email: wangshangcai@126.com; Tel/Fax: +86 10 8295 1320*

Abstract

Purpose: To evaluate the effectiveness and associated risks of rivaroxaban against warfarin in Chinese elderly diabetic patients with non-valvular atrial fibrillation.
Methods: Data regarding demographical characteristics, clinical conditions, ischemic stroke, intracranial bleeding, gastrointestinal tract bleeding, myocardial infractions, hip/pelvic fracture, asthma, breast/prostate cancer, and death during 3-years of treatment of 584 Chinese diabetic patients with confirmed non-valvular atrial fibrillation who were placed on rivaroxaban (RX Cohort, n = 201) or warfarin (WF Cohort, n = 383) were collected from hospital records and analyzed. Multivariate analysis was performed for the prediction of the incidence of the treatment-emergent event(s).
Results: During the 3-year treatment period, higher numbers of patients were reported for intracranial bleeding (p = 0.042), ischemic stroke (p = 0.042), gastrointestinal bleeding (p = 0.0006), hip/pelvic fracture (p = 0.042), and asthma (p = 0.0007) in WF cohort than RX cohort. Also, higher mortality was reported in WF cohort than for RX cohort (24 vs. 4, p = 0.024). Female sex (p = 0.031), age (p = 0.035), and comorbidities (p = 0.021) were associated with incidence of treatment-emergent event(s).
Conclusion: With rivaroxaban, a significant and safe risk-reduction of thromboembolic events are found in elderly diabetic patients with non-valvular atrial fibrillation.

Keywords: Anticoagulant, Diabetes, Non-valvular atrial fibrillation, Rivaroxaban, Warfarin

INTRODUCTION

Diabetes is a common morbidity associated with non-valvular atrial fibrillation [1] and has risk for combined endpoint events and mortality [2]. Diabetes has a greater risk of embolic events [3]. Unlike Caucasians, the prevalence of stroke in Chinese patients is associated with non-valvular atrial fibrillation and diabetes [4]. Approximately 8 million Chinese people are affected with non-valvular atrial fibrillation [2]. The current ACC/AHA/HRS (The American College of Cardiology/the American Heart Association/the Heart Rhythm Society) Guideline for the management of patients with non-valvular atrial fibrillation recommends the use of anticoagulants

[5] but the use of anticoagulants is less than 10 % in a Chinese population with a history of diabetes. Most of the patients received aspirin or nothing to prevent thromboembolism [6]. There is a big gap between the recommended guidelines and practice in China because antiplatelet is also frequently used instead of anticoagulant agents [4].

Warfarin is Vitamin K anticoagulant [7] and have been used for many years but warfarin treatment is contraindicated in elderly patients due to the risk of bleeding [4]. Also, United States Food and Drug Administration (FDA) in 2010 as an anticoagulant but has a high risk of intracranial and gastrointestinal tract bleeding [8]. Rivaroxaban is a factor Xa inhibitor and approved by FDA in 2011 as an anti-coagulant [9]. A once daily dose of 20 mg rivaroxaban is the recommended dose, 15 mg daily dose of rivaroxaban is recommended in patients with impaired kidney function, while a 10 mg daily dose of rivaroxaban is preferred in deep venous thrombosis. The primary objective of this retrospective analysis of prospectively collected data was to evaluate the effectiveness of rivaroxaban against warfarin in Chinese elderly diabetic patients with non-valvular atrial fibrillation. The secondary endpoint of the analysis was to evaluate the associated risks responsible for the treatment-emergent event(s).

METHODS

Ethics approval and consent to participate

The protocol of the established study was approved by the Huilongguan Community Health Service Center Human Ethics Committee (no. HCH/CL/15/19 dated 18 July 2019). The reporting of the analysis adheres to the law of China, the strengthening the reporting of observational studies in epidemiology (STROBE) cohort study: statement, and the 2008 Helsinki Declaration. The informed consent form was signed by all the enrolled patients or their relatives (legally authorized person) for interventions, pathology, and publication of work-up in all formats irrespective of time and language during hospitalization.

Inclusion criteria

Diabetic patients within the age of ≥ 60 years who had developed non-valvular atrial fibrillation (the arrhythmia duration > 7 days, confirmed by echocardiography [4]) and those the physician decided to put on any anticoagulant therapy were considered for the analysis.

Exclusion criteria

Non-diabetic patients, patients who had not developed non-valvular atrial fibrillation, and patients who had been on only antiplatelet therapies (e.g. aspirin, digoxin, and/or clopidogrel) were not considered for the analysis. Patients placed on any anticoagulants therapies but who had reduced kidney function were not considered for the analysis.

Interventions

Patients who received 20 mg rivaroxaban once in a day were considered for the RX Cohort and those who received 5 mg warfarin per day in two divided doses were included in the WF Cohort.

Outcome measures

Data regarding the event(s) of ischemic stroke, myocardial infractions, intracranial bleeding, gastrointestinal tract bleeding, breast/prostate cancer, hip/pelvic fracture, and asthma were collected from the institutional records. If patients had occlusion of cerebral arteries in imaging diagnosis (angiography and/or the Computed Tomography), it was considered as ischemic stroke. If patients had a subarachnoid hemorrhage in imaging diagnosis (angiography and/or the Computed Tomography), it was considered as intracranial bleeding. Clinical confirmation of gastrointestinal tract bleeding was carried out as per the published algorithm [10]. Myocardial infractions and breast/prostate cancer were evaluated by imaging diagnosis (angiography and/or the Computed Tomography) or biopsies wherever applicable. Hip/pelvic fracture was validated by the x-ray image. Asthma was defined by spirometry test of lung functions [11].

Statistical analysis

InStat window version 3.0, GraphPad, San Diego, CA, USA was used for statistical analysis. The Fisher's exact test was used for categorical variable and Mann-Whitney *U*-test was used for continuous variables. Multivariate analysis was performed for the prediction of the incidence of the treatment-emergent event(s). Data were considered significant at 95 % of confidence level.

RESULTS

Enrollment

From the 1st of June 2015 to 15th of June 2016, there were 920 diabetic patients recorded or

consulted in the outpatient center of the Huilongguan Community Health Service Center, Beijing, China and the referring hospitals. Among them, 85 patients had not developed non-valvular atrial fibrillation, therefore, they were not placed on anticoagulant or antiplatelet therapies. Also, 110 patients were below the age of 60 years. So, they were not considered for the analysis.

Among the remaining patients, 115 patients were placed on only antiplatelet therapies, so these were also excluded from the study and 26 patients who received anticoagulant therapy had reduced kidney functions. Therefore, they were not considered for the analysis. Data regarding outcome measures of 584 patients who were placed on rivaroxaban (RX Cohort, n = 201) or warfarin (WF Cohort, n = 383) were included in the analysis (Figure 1).
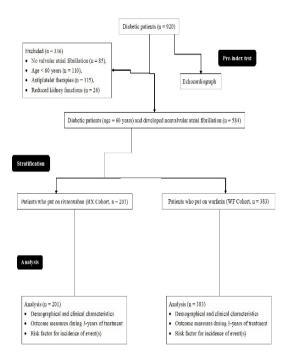

Figure 1: Flow chart of the analysis

Demographic characteristics

All the enrolled patients were new users of rivaroxaban or warfarin and no history of ischemic stroke, myocardial infractions, intracranial bleeding, gastrointestinal tract bleeding, breast/prostate cancer, and/ or hip/pelvic fracture. There was no significant difference between clinical and demographical characteristics for both groups at the start of anticoagulant therapy ($p < 0.05$ for all, Table 1).

Outcome measures

During 3-years of treatment, higher numbers of patients were reported for intracranial bleeding ($p = 0.042$), ischemic stroke ($p = 0.042$), gastrointestinal bleeding ($p = 0.0006$), hip/ pelvic fracture ($p = 0.042$), and asthma ($p = 0.0007$) in WF cohort than RX cohort (Table 2). Also, more numbers of death were reported in WF cohort than RX cohort (24 (6 %) vs. 4 (2 %), $p = 0.024$) during 3-years of the treatment period. No spine or wrist fracture and reduced kidney functions were reported in both cohorts' patients.

Risk factors for the incidence of treatment-emergent event(s)

Among the enrolled 584 patients of diabetes, 135 had reported one or more adverse events (stroke, bleeding, myocardial infarction, fracture, and/ or asthma) during 3-years of treatment. Among the risk factors, female sex ($p = 0.031$), age ($p = 0.035$) and comorbidities ($p = 0.021$) were associated with incidence of treatment-emergent event(s) (Table 3).

DISCUSSION

The study reported that diabetic patients with non-valvular atrial fibrillation who received rivaroxaban had the fewer risk of intracranial bleeding, ischemic stroke, and mortality than those who received warfarin during 3-years of treatment. The results of the study were consistent with the results of retrospective analysis [9] and a ROCKET trial on Caucasians patients [12]. With rivaroxaban, a significant risk reduction of thromboembolic events can be found in Chinese diabetic patients with non-valvular atrial fibrillation.

Fewer numbers of patients suffered from gastrointestinal bleeding in the cohort who received rivaroxaban than those received warfarin. The results of the study were parallel with the results of retrospective analyses [8-10] but were not consistent with a ROCKET trial on Caucasians patients [12]. Rivaroxaban is safe anticoagulant than warfarin.

Fewer numbers of patients suffered from hip/ pelvic fracture and asthma in a cohort who received rivaroxaban than those who received warfarin. The results of the study were parallel with the results of the retrospective analysis [9]. Warfarin inhibits the activation of bone proteins and impairs bone material hardness [13]. Hip/ pelvic fracture during 3-years of treatment is not an acceptable adverse effect hence rivaroxaban can be a good substitute for warfarin.

Table 1: Demographic and clinical characteristics

Parameter		Cohorts		Comparison between cohorts
		RX	WF	
		201	383	P-value
Gender	Male	119(59)	211(55)	0.38
	Female	82(21)	172(45)	
Age (years)	Minimum	60	60	
	Maximum	84	85	0.07
	Mean ± SD	69.52±4.55	68.69±5.56	
Ethnicity	Han Chinese	179(90)	357(93)	
	Tibetan	3(1)	4(1)	0.311
	Mongolian	17(8)	18(5)	
	North Korean refuge	2(1)	4(1)	
Body mass index (kg/m^2)	Minimum	23	22	
	Maximum	29	28	0.179
	Mean ± SD	25.12±2.11	24.89±1.88	
Hypertension		58(29)	139(36)	0.08
Dementia		11(5)	25(7)	0.719
Liver disease		4(2)	11(3)	0.6
Depression		17(8)	31(8)	0.875
Alcohol abuse	No	45(22)	88(23)	
	Previous	67(33)	129(34)	0.975
	Current	89(45)	166(43)	
Smoking	No	34(17)	61(16)	
	Previous	81(40)	152(40)	0.919
	Current	86(43)	170(44)	
Asthma (allergic or trace induced)		6(3)	10(3)	0.794
Diabetes medications		131(65)	225(59)	0.153
Hemoglobin (mg/dL)		11.45±1.21	11.78±2.45	0.07
% HbA1C		7.55±2.45	7.21±1.90	0.06

Continuous data are presented as mean ± SD and constant data are demonstrated as frequency (percentage). Fisher's exact test was used for constant variables and Mann-Whitney *U*-test for continuous variables. A *p*-value < 0.05 was considered significant

Table 2: Outcome measures during the 3-year treatment

Parameter	Cohort		Comparison between cohorts
	RX	WF	
	201	383	P-value
Intracranial bleeding	1(1)	12(3)*	0.042
Ischemic stroke	1(1)	13(3)*	0.042
Gastrointestinal bleeding	2(1)	28(7)*	0.0006
Myocardial infarction	1(1)	8(2)	0.175
Breast/ prostate cancer	1(1)	7(2)	0.274
Hip/ pelvic fracture	1(1)	13(3)*	0.042
Asthma	4(2)	35(9)*	0.0007

Variable are shown as frequency (percentage). Fisher's exact test was performed for statistical analysis; *p* < 0.05 was considered significant. *Significantly higher than RX cohort

Female sex, age, and the presence of comorbidities were responsible for stroke, bleeding, fracture, and the other treatment-emergent event(s). The results of the study were parallel with the results of the retrospective analysis [9]. Older women have comparatively fewer bone mass density than older men and younger women [14].

Table 3: Multivariate analysis for the incidence of treatment-emergent events (N = 135*)*

Risk factor	Confidence interval	P-value
Gender*	0.55–1.08	0.031
Age (years) *	0.56–1.12	0.035
Ethnicity	0.45–2.76	0.123
Body mass index (kg/m^2)	0.44–2.12	0.062
Comorbidity*	0.61–1.21	0.021
Alcohol abuse	0.57–2.89	0.089
Smoking	0.62–2.01	0.098
Diabetes medications	0.62–2.35	0.232
% HbA1C	0.63–1.89	0.095

Patients who showed no adverse event(s) were considered as the reference standard. A *p*-value < 0.05 was considered significant. *Significantly responsible for adverse event(s)

Diabetes with the other comorbidities increases the risk of stroke event(s) [3]. Anticoagulants always have the risk of bleeding [10]. The other independent risk factors responsible for stroke, bleeding, fracture, and the other event(s) are required to evaluate for treatment-emergent event(s).

Limitations of the study

There are several limitations of the analysis, for

example, the limited sample size has chances of type-I errors in the statistical analysis. The large randomized phase III trial is required to state the hypothesis strongly. The study is not completely generalized because the risk factors for the incidence of embolic events and treatment-emergent adverse effects are different in Caucasians and Chinese patients [1]. The quality of anticoagulation control was not possible because the treatment was for 3-years and the study lacks initial stage pathological results.

CONCLUSION

Warfarin is an effective treatment for embolic events in elderly Chinese patients with non-valvular atrial fibrillation but its management is difficult and has high adverse effects. Rivaroxaban appear to show a significant risk reduction of thromboembolic events with manageable treatment-emergent adverse effects.

DECLARATIONS

Acknowledgement

Conflict of interest

Authors declared that they have no conflict of interest or any the other competing interest regarding results and/or discussion reported in the research.

Authors' contributions

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. All authors read and approved the manuscript for publication. SW contributed to formal analysis and literature review of the study and draft, review, and edited the manuscript for intellectual content. RQ contributed to the project administration, investigation, data curation, validation, and literature review of the study. HZ contributed to conceptualization, supervision, resources, data curation, and literature review of the study. The authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Open Access

REFERENCES

1. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, Maclehose R, Konety S, Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: The Atherosclerosis Risk in Communities (ARIC) study. Circulation 2011; 123(14): 1501–1518.

2. Huang B, Yang Y, Zhu J, Liang Y, Zhang H, Tian L, Shao X, Wang J. Clinical characteristics and impact of diabetes mellitus on outcomes in patients with nonvalvular atrial fibrillation. Yonsei Med J 2015; 56(1): 62–71.

3. Brambatti M, Darius H, Oldgren J, Clemens A, Noack HH, Brueckmann M, Yusuf S, Wallentin L, Ezekowitz MD, Connolly SJ, et al. Comparison of dabigatran versus warfarin in diabetic patients with atrial fibrillation: Results from the RE-LY trial. Int J Cardiol 2015; 196: 127–131.

4. Sun Y, Hu D, Li K, Zhou Z. Predictors of stroke risk in native Chinese with nonrheumatic atrial fibrillation: Retrospective investigation of hospitalized patients. Clin Cardiol 2009; 33(2): 76–81.

5. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64(21): e1–e76.

6. Xiang W, Zhang J., Liu M, Liu F, Feng X, Wang Y. Antithrombotic therapy in elderly patients with non-valvular atrial fibrillation: A pilot study. Clin Interv Aging 2015; 10: 515–519.

7. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, et al. Vitamin K antagonists in heart disease: Current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thromb Haemost 2013; 110(6): 1087–1107.

8. Lip GY, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R, Hamilton M. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation

patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. Thromb Haemost 2016; 116(5): 975–986.

9. Norby FL, Bengtson LG, Lutsey PL, Chen LY, MacLehose RF, Chamberlain AM, Rapson I, Alonso A. Comparative effectiveness of rivaroxaban versus warfarin or dabigatran for the treatment of patients with non-valvular atrial fibrillation. BMC Cardiovasc Disord 2017; 17(1). DOI: 10.1186/s12872-017-0672-5.

10. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf 2011; 20(6): 560–566.

11. Salem AM, Bamosa AO, Qutub HO, Gupta RK, Badar A, Elnour A, Afzal MN. Effect of Nigella sativa supplementation on lung function and inflammatory mediators in partly controlled asthma: A randomized controlled trial. Ann Saudi Med 2017; 37(1): 64–71.

12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365(10): 883–891.

13. Sugiyama T, Kugimiya F, Kono S, Kim YT, Oda H. Warfarin use and fracture risk: An evidence-based mechanistic insight. Osteoporos Int 2015; 26(3): 1231–1232.

14. Sugiyama T, Takaki T, Sakanaka K, Sadamaru H, Mori K, Kato Y, Taguchi T, Saito T. Warfarin-induced impairment of cortical bone material quality and compensatory adaptation of cortical bone structure to mechanical stimuli. J Endocrinol 2007; 194(1): 213–222.