Supplemental Materials

Low-Dose Rivaroxaban and Risks of Adverse Events in Patients with Atrial Fibrillation

Wen-Han Cheng, M.D.[1,2], Tze-Fan Chao, M.D.[1, 2], Yenn-Jiang Lin, M.D.[1,2], Shih-Lin Chang, M.D.[1,2], Li-Wei Lo, M.D.[1,2], Yu-Feng Hu, M.D.[1,2], Ta-Chuan Tuan, M.D.[1,2], Jo-Nan Liao, M.D.[1,2], Fa-Po Chung, M.D. [1,2], Gregory Y. H. Lip, M.D.[3*], Shih-Ann Chen, M.D.[1,2*]

[1]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan. [2]Institute of Clinical Medicine, and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan. [3]Liverpool Centre for Cardiovascular Science, University of Liverpool & Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

[*Joint senior authors]

Running title: Outcomes of low dose rivaroxaban

Address for Correspondence

Tze-Fan Chao, M.D.

Division of Cardiology, Taipei Veterans General Hospital

201, Sec. 2, Shih-Pai Road, Taipei, Taiwan

Tel: 886-2-2875-7156; Fax: 886-2-2875-5656; E-mail: eyckeyck@gmail.com

Methods

Analysis of net clinical benefit (NCB)

The NCB for the use of on-label dose rivaroxaban compared with off-label low-dose rivaroxaban was calculated using the formula: (ischemic stroke rate on off-label low-dose rivaroxaban minus ischemic stroke rate on on-label dose rivaroxaban) – weighting factor x (ICH (intra-cranial hemorrhage) rate on on-label dose rivaroxaban minus ICH rate on off-label low-dose rivaroxaban). The weighting factor reflects the relative impact, in terms of death and disability, of an ICH versus experiencing an ischemic stroke.[1-3] The NCB with 95% confidence intervals (CI) were calculated from rate differences of ischemic stroke and ICH of the present study based on the weights previously produced and reported in the studies by Singer et al.,[1] Connolly et al.,[2] and Lip et al.[3] A positive NCB favors on-label dose rivaroxaban when compared to off-label low-dose rivaroxaban.

Propensity match analysis

We performed propensity score-matched analyses for comparisons between the two groups: "on-label dose versus off-label low-dose". We calculated propensity scores for the likelihoods of receiving the on-label dose rivaroxaban compared to the off-label low-dose rivaroxaban by multivariate logistic regression analyses, conditional on all baseline covariates listed in Table 1. After that, we matched patients in the off-label low-dose group to those in the on-label dose group with a 1:1 ratio on the basis of the closest propensity score for the use of on-label dose rivaroxaban within a threshold of ±0.01 using the greedy algorithm. If more than one patient in the on-label dose group could be matched to the corresponding subject in the off-label low-dose group, 1 patient from the on-label dose group was selected randomly without repeat sampling.

Statistical analysis

Data were presented as the mean value and standard deviation (SD) for continuous variables, proportions for categorical variables. Differences between continuous values were assessed using the unpaired two-tailed t-test, and differences between nominal variables were compared by the chi-squared test. The incidences of ischemic stroke and ICH were calculated from dividing the number of event by person-time at risk. The risks of ischemic stroke and ICH between on-label dosing and off-label low-dosing groups were compared using the Cox regression analysis in an intention to treat design counting all events (whether on or off drugs), similar to most clinical trials. The proportional hazards assumption was tested using Schoenfeld residual test which showed no non-proportionality. The cumulative incidence curves of events were plotted via the Kaplan-Meier method, with statistical significance examined by the log-rank test. All statistical significances were set at a $p < 0.05$.

Supplemental Table I. Multivariate analysis between on-label dose and off-label low-dose groups

	Multivariate analysis*	
Variables	**OR (95% CI)**	***P* value**
Age ≥ 75 years	1.73 (1.35 – 2.23)	< 0.001
CHA_2DS_2-VASc score >=2	1.65 (1.17 – 2.33)	0.004
Comorbidities		
COPD	1.18 (0.85 – 1.63)	0.328
Liver cirrhosis	2.80 (1.09 – 7.19)	0.033
History of ICH	2.49 (1.07 – 5.78)	0.033
History of GI bleeding	1.28 (0.90 – 1.82)	0.172

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GI bleeding = gastro-intestinal bleeding; ICH = intra-cranial hemorrhage; OR = odds ratio

*Variables with a p value < 0.05 in the univariate logistic regression model were included in the multivariate model

Supplemental Table II. The net clinical benefit analyses for each treatment according to different weight models

Stroke prevention strategy	NCB based on different weight models, % per year (95% CI)		
	Relative weight of ICH compared to ischemic stroke according to Singer et al.[1] Weight = 1.5	Relative weight of ICH compared to ischemic stroke according to Connolly et al.[2] Weight = 3.08	Relative weight of ICH compared to ischemic stroke according to Lip et al.[3] Weight = 2.44
Compared to off-label low dose (n = 584) (reference group)	_	_	_
On-label dose (n = 1630)	1.90 (1.76 to 2.05)	1.87 (1.82 to 2.34)	1.88 (1.54 to 1.97)

CI = confidence interval; ICH = intra-cranial hemorrhage; NCB = net clinical benefit

Supplemental Table III. Baseline characteristics of patients after propensity match

Variables	All patients (n =1,030)	On-label dose (n = 515)	Off-label low dose (n =515)	P value*
Age, years; mean value (SD)	77.9 (11.1)	78.0 (11.1)	77.8 (11.2)	0.782
Age ≥ 75 years, *n* (%)	694 (67.4)	352 (68.3)	342 (66.4)	0.507
Age 65–74 years, *n* (%)	213 (20.7)	101 (19.6)	112 (21.7)	0.398
Male gender, *n* (%)	621 (60.3)	308 (59.8)	313 (60.8)	0.750
Paroxysmal AF, *n* (%)	163 (15.8)	81 (15.7)	82 (15.9)	0.932
CHA_2DS_2-VASc score; mean values (SD)	3.09 (1.42)	3.10 (1.47)	3.08 (1.39)	0.827
Warfarin naïve, *n* (%)	730 (70.9)	354 (68.7)	376 (73.0)	0.132
Concurrent use of antiplatelet agents, *n* (%)	252 (24.5)	126 (24.5)	126 (24.5)	1.000
Comorbidities, *n* (%)				
Hypertension	605 (58.7)	302 (58.6)	303 (58.8)	0.950

Diabetes mellitus	221 (21.5)	109 (21.2)	112 (21.7)	0.820
Heart failure	263 (25.5)	133 (25.8)	130 (25.2)	0.830
Previous stroke/TIA	22 (2.1)	11 (2.1)	11 (2.1)	1.000
Vascular diseases	104 (10.1)	54 (10.5)	50 (9.7)	0.679
COPD	98 (9.5)	47 (9.1)	51 (9.9)	0.671
Malignancy	173 (16.8)	87 (16.9)	86 (16.7)	0.934
Liver cirrhosis	9 (0.9)	5 (1.0)	4 (0.8)	0.738
History of ICH	12 (1.2)	5 (1.0)	7 (1.4)	0.562
History of GI bleeding	81 (7.9)	39 (7.6)	42 (8.2)	0.729
History of blood transfusion	110 (10.7)	60 (11.7)	50 (9.7)	0.314
eGFR; mean values (SD)	73.49 (18.2)	73.53 (20.8)	73.44 (15.2)	0.939
Propensity score; mean values (SD)	0.29 (0.10)	0.29 (0.10)	0.29 (0.10)	0.993

AF = atrial fibrillation; eGFR = estimated glomerular filtration rate; GI bleeding = gastro-intestinal bleeding; ICH = intracranial hemorrhage; SD = standard deviation; TIA = transient ischemic attack

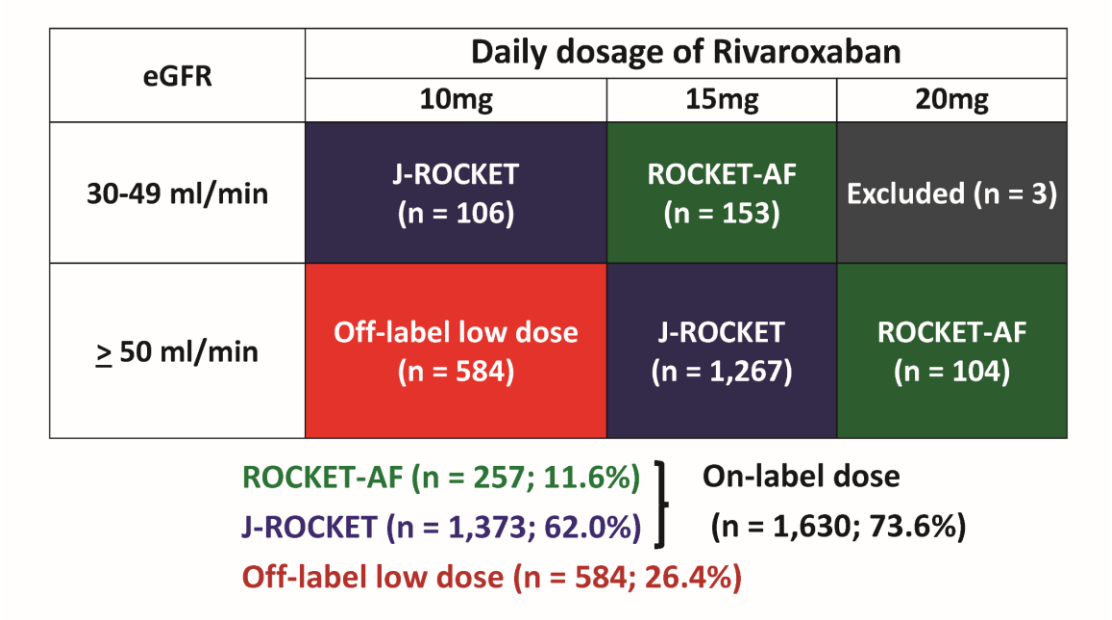
*P values comparing on-label and off-label dosing groups

Figure legend

Supplemental Figure I. Distributions of patients in different dosing groups. Study patients were divided into 2 groups – (1) on-label dosing group (n = 1,630; 73.6%) – patients received daily dose of rivaroxaban according to ROCKET-AF (20mg/day for patients with an eGFR ≥50 ml/min and 15mg/day for those with an eGFR=30-49 ml/min; n = 257) or J-ROCKET (15mg/day for patients with an eGFR ≥50 ml/min and 10mg/day for those with an eGFR=30-49 ml/min; n = 1373) studies; and (2) off-label low-dosing group (n = 584; 26.4%) - rivaroxaban at a daily dose of 10mg for patients with an eGFR ≥50 ml/min.

eGFR = estimated glomerular filtration rate;

Supplemental Figure I



References

1. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med* 2009;151:297-305.

2. Connolly SJ, Eikelboom JW, Ng J, Hirsh J, Yusuf S, Pogue J, et al. Net clinical benefit of adding clopidogrel to aspirin therapy in patients with atrial fibrillation for whom vitamin K antagonists are unsuitable. *Ann Intern Med* 2011;155:579-586.

3. Lip GY, Skjoth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. *Thromb Haemost* 2015;114:826-834.