Comparisons of Effectiveness and Safety between On-label Dosing, Off-label Underdosing and Off-label Overdosing in Asian and Non-Asian Atrial Fibrillation Patients Treated with Rivaroxaban: a Systematic Review and Meta-analysis of Observational Studies

Chan, Yi-Hsin; Chan, Chih-Yu; Chen, Shao-Wei; Chao, Tze-Fan; Lip, Gregory Y. H.

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META-ANALYSIS

Comparisons of effectiveness and safety between on-label dosing, off-label underdosing, and off-label overdosing in Asian and non-Asian atrial fibrillation patients treated with rivaroxaban: a systematic review and meta-analysis of observational studies

Yi-Hsin Chan [1,2,3], Chih-Yu Chan [2], Shao-Wei Chen [4], Tze-Fan Chao [5,6]*†, and Gregory Y.H. Lip [7,8]†

[1]Cardiovascular Department, Chang Gung Memorial Hospital, Linkou, Taoyuan 33305, Taiwan; [2]College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan; [3]Microscopy Core Laboratory, Chang Gung Memorial Hospital, Linkou, Taoyuan 33305, Taiwan; [4]Division of Thoracic and Cardiovascular Surgery, Department of Surgery, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University, Taoyuan, Taiwan; [5]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei 11217, Taiwan; [6]Institute of Clinical Medicine, Cardiovascular Research Center, National Yang Ming Chiao Tung University, Taipei 112304, Taiwan; [7]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK; and [8]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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Aims

Limited real-world data show that rivaroxaban following dosage criteria from either ROCKET AF [20 mg/day or 15 mg/day if creatinine clearance (CrCl) < 50 mL/min] or J-ROCKET AF (15 mg/day or 10 mg/day if CrCl < 50 mL/min) is associated with comparable risks of thromboembolism and bleeding with each other in patients with non-valvular atrial fibrillation (NVAF). We are aimed to study whether these observations differ between Asian and non-Asian subjects.

Methods and results

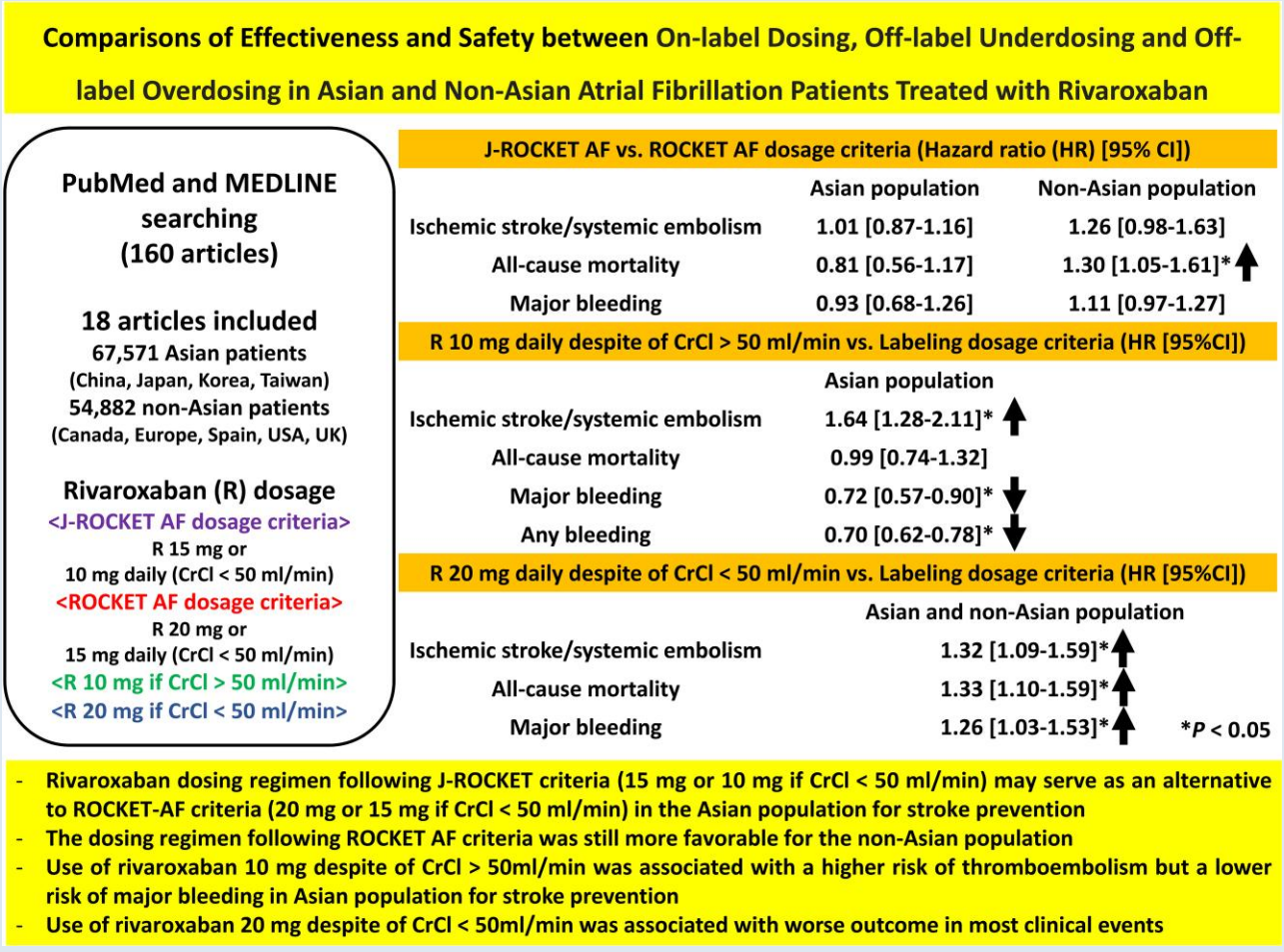
A systematic review and meta-analysis with random effects was conducted to estimate the aggregate hazard ratio (HR) and 95% confidence interval (CI) using PubMed and MEDLINE databases from 8 September 2011 to 31 December 2022 searched for adjusted observational studies that reported relevant clinical outcomes of NVAF patients receiving rivaroxaban 10 mg/day if CrCl > 50 mL/min, on-label dose rivaroxaban eligible for ROCKET AF or J-ROCKET AF, and rivaroxaban 20 mg/day if CrCl < 50 mL/min. Effectiveness and safety endpoints were compared between ROCKET AF and J-ROCKET AF dosing regimen in Asian and non-Asian subjects, separately. Also, risks of events of rivaroxaban 10 mg/day despite of CrCl > 50 mL/min and rivaroxaban 20 mg/day despite of CrCl < 50 mL/min were compared to that of 'ROCKET AF/J-ROCKET AF dosing'. Sensitivity analyses were performed by sequential elimination of each study from the pool. The meta-regression analysis was performed to explore the influence of potential factors on the effectiveness and safety outcomes. Eighteen studies involving 67 571 Asian and 54 882 non-Asian patients were included. Rivaroxaban following J-ROCKET AF criteria was associated with comparable risks of thromboembolism in the Asian subgroup, whereas rivaroxaban following J-ROCKET AF criteria was associated with higher risks of all-cause mortality (HR:1.30; 95% CI:1.05–1.60) compared with that of ROCKET AF criteria in the non-Asian population. There were no differences in risks of major bleeding between rivaroxaban following J-ROCKET AF vs. ROCKET AF criteria either in the Asian or non-Asian population. The use of rivaroxaban 10 mg despite of CrCl > 50 mL/min was associated with a higher risk of thromboembolism (HR:1.64; 95% CI:1.28–2.11) but lower risk of major bleeding (HR:0.72; 95% CI:0.57–0.90) compared with eligible dosage

* Corresponding author. Tel: 886 2 2875 7156; fax: 886 2 2875 5656. *E-mail address*: eyckeyck@gmail.com
† Tze-Fan Chao, MD, PhD and Gregory Y.H. Lip, MD are joint senior authors.

criteria. The use of rivaroxaban 20 mg despite of CrCl < 50 mL/min was associated with worse clinical outcomes in the risks of thromboembolism (HR:1.32; 95% CI:1.09–1.59), mortality (HR:1.33; 95% CI:1.10–1.59), and major bleeding (HR:1.26; 95% CI:1.03–1.53) compared with eligible dosage criteria. The pooled results were generally in line with the primary effectiveness and safety outcomes by removing a single study at one time. Meta-regression analyses failed to detect the bias in most potential patient characteristics associated with the clinical outcomes.

Conclusion Rivaroxaban dosing regimen following J-ROCKET criteria may serve as an alternative to ROCKET AF criteria for the Asian population with NVAF, whereas the dosing regimen following ROCKET AF criteria was more favourable for the non-Asian population. The use of rivaroxaban 10 mg despite of CrCl > 50 mL/min was associated with a higher risk of thromboembolism but a lower risk of major bleeding, while use of rivaroxaban 20 mg despite of CrCl < 50 mL/min was associated with worse outcome in most clinical events.

Graphical Abstract



Keywords Atrial fibrillation • Factor Xa inhibitor • Mortality • Ischaemic stroke • Major bleeding • Major gastrointestinal bleeding • Intracranial haemorrhage • Rivaroxaban • Warfarin

Introduction

The global ROCKET AF study was the pivotal study that investigated the efficacy and safety of rivaroxaban 20 mg daily [15 mg daily if serum creatinine clearance (CrCl) < 50 mL/min] compared to warfarin therapy for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). The trial results showed that rivaroxaban was associated with a comparable risk of stroke/systemic embolism and major bleeding to warfarin in patients with NVAF.[1] The J-ROCKET AF trial was a similar but much smaller study to compare the efficacy and safety of rivaroxaban 15 mg daily [10 mg daily if creatinine clearance (CrCl) < 50 mL/min] and warfarin in Japanese with NVAF, which also showed a comparable risk of thromboembolism and major bleeding with rivaroxaban 15/10 mg daily vs. warfarin.[2] Recent meta-analysis has shown that a higher prevalence (~22%) of off-label underdosed rivaroxaban was commonly prescribed in patients with NVAF worldwide (e.g. use of rivaroxaban 15 mg daily

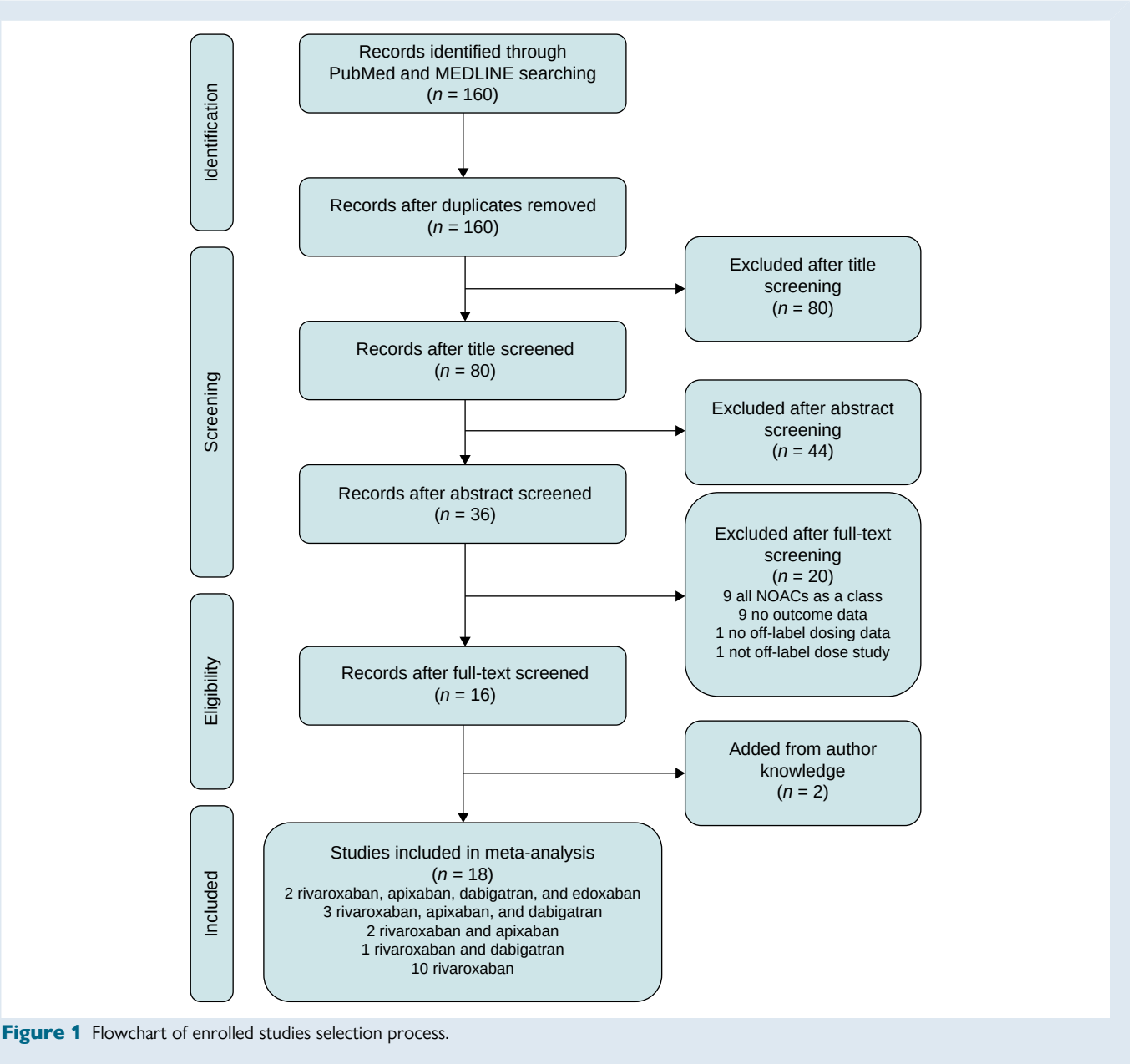


Figure 1 Flowchart of enrolled studies selection process.

despite of CrCl > 50 mL/min, which was not eligible for the ROCKET AF dosage criteria but eligible for the J-ROCKET AF dosage criteria),[3] allowing the opportunity to investigate the effectiveness and safety between the two dosage criteria worldwide. In the present study, we aimed to perform a systematic review of the available real-world evidence or prospective registries to compare relevant clinical outcomes of AF patients receiving off-label underdosing rivaroxaban (10 mg daily if CrCl > 50 mL/min), on-label dose rivaroxaban eligible for ROCKET AF or J-ROCKET AF, and off-label overdosing rivaroxaban (20 mg daily if CrCl < 50 mL/min) specifically focused on Asian or non-Asian population separately.

Methods

Search strategy and inclusion criteria

We followed the PRISMA (preferred reporting items for systematic reviews and meta-analyses) and MOOSE (Meta-analyses of Observational Studies in Epidemiology) guidelines when performing the meta-analyses.[4,5] Two independent reviewers (Y.-H.C. and C.-Y.C.) conducted a comprehensive search of PubMed and Medline between 8 September 2011 and 31 December 2022. The search items were (rivaroxaban) AND (atrial fibrillation) AND (inappropriate OR off-label OR underdose OR underdosing OR overdose OR overdosing OR non-recommended dose OR non-recommended dosing). We included prospective or retrospective studies comparing rivaroxaban following different dose regimen with each other.

Outcome measures

The assessed outcomes included thromboembolism (ischaemic stroke/stroke or systemic embolism), all-cause mortality, major bleeding, intracranial haemorrhage (ICH), gastrointestinal bleeding (GIB), and any bleeding.

Quality assessment

Two researchers (Y.-H.C. and C.-Y.C.) independently extracted study data using a predetermined form and assessed the quality of observational studies using the Newcastle–Ottawa Scale, which evaluates the selection of

Table 1 Information of the included studies

Author	Region	Enrolled period	Data source	Primary statistical method	Number of patients treated with rivaroxaban[a]	Number of patients treated with rivaroxaban eligible for J-ROCKET AF[a]	Number of patients treated with rivaroxaban eligible for ROCKET AF[a]	Number of patients treated with rivaroxaban 10 mg despite of CrCl > 50 mL/min[a]	Number of patients treated with rivaroxaban 20 mg despite of CrCl < 50 mL/min[a]
Amarenco *et al.* 2019[6]	Europe, Canada, Israel	2012–2013	The XANTUS (prospective)	MLR	6784	583	3608	NR	232
Atarashi *et al.* 2021[7]	Japan	2013–2014	The EXPAND (prospective)	PSM	6806	5089	108	1609	NR
Kim *et al.* 2021[8]	Korea	2012–2017	Hospital-based electrical medical database (retrospective)	PSM	283	177	106	NR	NR
Yagi *et al.* 2020[9]	Japan	2012–2017	Hospital-based electrical medical database (retrospective)	Not adjusted	631	500	8	123	NR
Cho *et al.* 2020[10]	Korea	2015–2016	National Health Insurance Service database (retrospective)	IPTW	9639	4879	4760	NR	NR
González-Pérez *et al.* 2022[11]	UK	2012–2018	IQVIA Medical Research Data UK database (retrospective)	MLR	14 284	888	12 590	NR	806
Alcusky *et al.* 2020[12]	USA	2011–2016	Medicare beneficiaries database (retrospective)	MLR	3735	1647	1658	NR	430
Ikeda *et al.* 2019[15]	Japan	2012–2014	The XAPASS (prospective)	IPTW	6521	4185	NR	2336	NR
Yu *et al.* 2020[16]	Korea	2013–2016	National Health Insurance Service database (retrospective)	MLR	20 143	5426	12 332	NR	2385
Arashi *et al.* 2020[17]	Japan	2015–2017	The AFIRE (prospective)	PSM	1378	1022	NR	356	NR

Continued

Table 1 *Continued*

Author	Region	Enrolled period	Data source	Primary statistical method	Number of patients treated with rivaroxaban[a]	Number of patients treated with rivaroxaban eligible for J-ROCKET AF[a]	Number of patients treated with rivaroxaban eligible for ROCKET AF[a]	Number of patients treated with rivaroxaban 10 mg despite of CrCl > 50 mL/min[a]	Number of patients treated with rivaroxaban 20 mg despite of CrCl < 50 mL/min[a]
Briasoulis *et al.* 2020[18]	USA	2010–2016	Medicare beneficiaries database (retrospective)	PSM	19 712	2551	13 257	NR	3904
Lee *et al.* 2019[19]	Korea	2014–2016	National Health Insurance Service database (retrospective)	PSM	13 594	5796	7798	NR	NR
Xu *et al.* 2022[20]	China	2016–2020	Hospital-based electrical medical database (retrospective)	PSM	1227	890	337	NR	NR
Yao *et al.* 2017[21]	USA	2010–2015	OptumLabs Data Warehouse (retrospective)	PSM	6428	815	5188	NR	425
Ashraf *et al.* 2021[22]	USA	2001–2017	Hospital-based electrical medical database (retrospective)	MLR	2518	440	2078	NR	NR
Chan *et al.* 2020[23]	Taiwan	2012–2018	Hospital-based electrical medical database (retrospective)	MLR	5135	2837	1354	858	86
Cheng *et al.* 2021[24]	Taiwan	2012–2016	Hospital-based electrical medical database (retrospective)	MLR	2214	1373	257	584	NR
Fernandez *et al.* 2021[25]	Spain	2016–2019	The EMIR (prospective)	MLR	1421	138	1183	NR	100

NR, not reported; APT, antiplatelet agent; BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischaemic attack, vascular disease, age 65 to 74 years, female; CKD, chronic kidney disease; CrCl, creatinine clearance rate; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age 65 years or older, and antiplatelet drug or alcohol use; IPTW, inverse probability of treatment weighting; MLR, multivariable logistic regression; PSM, propensity score matching; sCr, serum creatinine.

[a]Crude patient number before adjustment.

Continued

Table 1 *Continued*

Author	Age (mean)	Female (%)	Body weight (kg)	BMI (kg/m^2)	CrCl (mL/min)	CKD or CrCl < 50	CHA_2DS_2-VASc	HAS-BLED	Bleeding history	Heart failure	Hypertension	Diabetes	Stroke or TIA	Vascular disease	Dyslipidaemia	Use of APT
Amarenco *et al.* 2019[6]	71.5	41	83.0	28.2	NR	9%	3.4	NR	NR	19%	75%	20%	19%	10%	NR	18%
Atarashi *et al.* 2021[7]	71.6	32	62.7	NR	NR	22%	3.4	1.4	4%	27%	71%	25%	24%	4%	42%	9%
Kim *et al.* 2021[8]	72.5	45	NR	NR	NR	NR	3.3	NR	NR	9%	63%	24%	20%	11%	NR	NR
Yagi *et al.* 2020[9]	69.1	22	67.1	NR	75.4	16%	2.2	1.5	NR	17%	54%	16%	6%	5%	31%	11%
Cho *et al.* 2020[10]	69.8	40	NR	25.5	72.7	2%	3.3	2.4	NR	19%	89%	47%	2%	11%	NR	9%
González-Pérez *et al.* 2022[11]	74.9	43	NR	NR	NR	42%	3.4	1.7	27%	16%	67%	NR	13%	27%	NR	46%
Alcusky *et al.* 2020[12]	84	69	NR	NR	NR	19%	5	3*	NR	33%	84%	35%	23%	26%	NR	23%
Ikeda *et al.* 2019[15]	69.5	31	65.3	24.8	78.8	0%	3.1	1.3	NR	21%	74%	23%	21%	3%	NR	13%
Yu *et al.* 2020[16]	70.5	40	NR	NR	NR	8%	4.6	NR	NR	61%	96%	32%	46%	29%	92%	16%
Arashi *et al.* 2020[17]	71.4	14	68.6	25.4	74.3	0%	3.7	2.1	1%	30%	87%	45%	13%	34%	71%	36%
Briasoulis *et al.* 2020[18]	NR	50	NR	NR	NR	47%	NR	NR	25%	28%	93%	49%	24%	43%	NR	26%
Lee *et al.* 2019[19]	71.2	45	63.8	24.7	82.3	0%	3.5	NR	0%	30%	72%	22%	0%	3%	42%	NR
Xu *et al.* 2022[20]	64.2	43	65.8	NR	75.8	NR	2.1	1.3	NR	5%	81%	26%	2%	7%	NR	NR
Yao *et al.* 2017[21]	70.6	43	NR	NR	69.9	17%	NR	NR	11%	40%	90%	42%	14%	28%	82%	8%
Ashraf *et al.* 2021[22]	73.8	44	NR	30.6	sCr: 1.1	17%	3.7	2.4+	NR	NR	83%	28%	22%	29%	66%	NR
Chan *et al.* 2020[23]	74.2	42	65.4	NR	60.9	25%	3.5	2.8	NR	11%	75%	34%	17%	12%	43%	54%
Cheng *et al.* 2021[24]	75.7	36	NR	NR	71.3	NR	2.9	NR	8%	25%	57%	22%	2%	9%	NR	24%
Fernandez *et al.* 2021[25]	74.2	44	79.7	29.1	76.0	16%	3.5	1.6	3%	23%	79%	27%	13%	17%	55%	8%

Continued

Table 1 *Continued*

Author	IS/SE[a] (rate per 100 PYs)	Mortality[a] (rate per 100 PYs)	Major bleeding[a] (rate per 100 PYs)
Amarenco *et al.* 2019[6]	1.9 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF) 2.7 (15 mg if CrCl > 50; J-ROCKET AF) 2.9 (20 mg if CrCl < 50)	1.9 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF) 3.1 (15 mg if CrCl > 50; J-ROCKET AF) 3.8 (20 mg if CrCl < 50)	2.6 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF) 3.9 (15 mg if CrCl > 50; J-ROCKET AF) 2.9 (20 mg if CrCl < 50)
Atarashi *et al.* 2021[7]	1.57 (15 mg if CrCl < 50; ROCKET AF) 0.83 (15 mg if CrCl > 50; J-ROCKET AF) 1.46 (10 mg if CrCl < 50; J-ROCKET AF) 0.88 (10 mg if CrCl > 50)	5.09 (15 mg if CrCl < 50; ROCKET AF) 0.75 (15 mg if CrCl > 50; J-ROCKET AF) 3.69 (10 mg if CrCl < 50; J-RCOKET AF) 1.67 (10 mg if CrCl > 50)	3.53 (15 mg if CrCl < 50; ROCKET AF) 1.01 (15 mg if CrCl > 50; J-ROCKET AF) 1.80 (10 mg if CrCl < 50; J-ROCKET AF) 1.13 (10 mg if CrCl > 50)
Kim *et al.* 2021[8]	1.9 (20 mg if CrCl > 50; ROCKET AF) 2.8 (15 mg if CrCl > 50; J-ROCKET AF)	0.9 (20 mg if CrCl > 50; ROCKET AF) 1.7 (15 mg if CrCl > 50; J-ROCKET AF)	0.9 (20 mg if CrCl > 50; ROCKET AF) 2.3 (15 mg if CrCl > 50; J-ROCKET AF)
Yagi *et al.* 2020[9]	0.0 (15 mg if CrCl < 50; ROCKET AF) 0.1 (15 mg if CrCl > 50; J-ROCKET AF) 0.0 (10 mg if CrCl < 50; J-ROCKET AF) 0.0 (10 mg if CrCl > 50)	0.0 (15 mg if CrCl < 50; ROCKET AF) 0.3 (15 mg if CrCl > 50; J-ROCKET AF) 0.9 (10 mg if CrCl < 50; J-ROCKET AF) 0.8 (10 mg if CrCl > 50)	0.0 (15 mg if CrCl < 50; ROCKET AF) 0.7 (15 mg if CrCl > 50; J-ROCKET AF) 1.9 (10 mg if CrCl < 50; J-ROCKET AF) 0.8 (10 mg if CrCl > 50)
Cho *et al.* 2020[10]	2.0 (20 mg if CrCl > 50; ROCKET AF) 2.5 (15 mg if CrCl > 50; J-ROCKET AF)	1.7 (20 mg if CrCl > 50; ROCKET AF) 1.9 (15 mg if CrCl > 50; J-ROCKET AF)	1.7 (20 mg if CrCl > 50; ROCKET AF) 2.2 (15 mg if CrCl > 50; J-ROCKET AF)
González-Pérez *et al.* 2022[11]	1.7 (20 mg if CrCl < 50; overdosing)[d] 1.1 (20 mg if CrCl > 50; ROCKET AF)[d] 1.5 (15 mg if CrCl < 50; ROCKET AF)[d] 2.4 (15 mg if CrCl > 50; J-ROCKET AF)[d]	19.4 (20 mg if CrCl < 50; overdosing)[d] 7.3 (20 mg if CrCl > 50; ROCKET AF)[d] 23.1 (15 mg if CrCl < 50; ROCKET AF)[d] 32.0 (15 mg if CrCl > 50; J-ROCKET AF)[d]	NR
Alcusky *et al.* 2020[12]	1.75 (2011–2013)[b] 1.89 (2014–2016)[b]	28.18 (2011–2013)[b] 31.17 (2014–2016)[b]	6.22 (2011–2013)[b] 6.58 (2014–2016)[b]
Ikeda *et al.* 2019[15]	1.5 (15 or 10 mg if CrCl > 50 or <50; J-ROCKET AF)[c] 2.2 (10 mg if CrCl > 50)[c]	NR	1.6 (15 or 10 mg if CrCl > 50 or <50; J-ROCKET AF)[c] 1.3 (10 mg if CrCl > 50)[c]
Yu *et al.* 2020[16]	5.8 (20 mg if CrCl < 50) 4.0 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF) 4.0 (15 if CrCl > 50; J-ROCKET AF)	5.4 (20 mg if CrCl < 50) 3.1 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF) 3.2 (15 if CrCl > 50; J-ROCKET AF)	4.8 (20 mg if CrCl < 50) 2.9 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF) 3.0 (15 if CrCl > 50; J-ROCKET AF)
Arashi *et al.* 2020[17]	1.1 (15 or 10 mg if CrCl > 50 or <50; J-ROCKET AF) 0.7 (10 mg if CrCl > 50)	1.4 (15 or 10 mg if CrCl > 50 or <50; J-ROCKET AF) 1.6 (10 mg if CrCl > 50)	2.2 (15 or 10 mg if CrCl > 50 or <50; J-ROCKET AF) 0.8 (10 mg if CrCl > 50)
Briasoulis *et al.* 2020[18]	4.3 (20 mg if CrCl < 50) 2.6 (20 mg if CrCl > 50; ROCKET AF) 5.7 (15 mg if CrCl < 50; ROCKET AF) 4.0 (15 mg if CrCl > 50; J-ROCKET AF)	NR	7.9 (20 mg if CrCl < 50) 4.3 (20 mg if CrCl > 50; ROCKET AF) 9.9 (15 mg if CrCl < 50; ROCKET AF) 6.7 (15 mg if CrCl > 50; J-ROCKET AF)
Lee *et al.* 2019[19]	2.2 (20 mg if CrCl > 50; ROCKET AF)[c] 2.6 (15 mg if CrCl > 50; J-ROCKET AF)[c]	3.6 (20 mg if CrCl > 50; ROCKET AF)[c] 4.3 (15 mg if CrCl > 50; J-ROCKET AF)[c]	2.3 (20 mg if CrCl > 50; ROCKET AF)[c] 2.7 (15 mg if CrCl > 50; J-ROCKET AF)[c]
Xu *et al.* 2022[20]	0.6 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF)[d] 1.8 (15 if CrCl > 50; J-ROCKET AF)[d]	9.2 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF)[d] 2.9 (15 if CrCl > 50; J-ROCKET AF)[d]	2.4 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF)[d] 0.2 (15 if CrCl > 50; J-ROCKET AF)[d]
Yao *et al.* 2017[21]	2.8 (20 mg if CrCl < 50)[c] 1.7 (20 mg if CrCl > 50; ROCKET AF)[c] 1.2 (15 mg if CrCl < 50; ROCKET AF)[c] 1.2 (15 mg if CrCl > 50; J-ROCKET AF)[c]	NR	11.0 (20 mg if CrCl < 50)[c] 4.9 (20 mg if CrCl > 50; ROCKET AF)[c] 5.9 (15 mg if CrCl < 50; ROCKET AF)[c] 5.4 (15 mg if CrCl > 50; J-ROCKET AF)[c]
Ashraf *et al.* 2021[22]	18.9 for 5 years (on-label)[d,e] 22.4 for 5 years (underdosing)[d,e]	13.0 for 5 years (on-label)[d,e] 18.7 for 5 years (underdosing)[d,e]	8.3 for 5 years (on-label)[d,e] 10.2 for 5 years (underdosing)[d,e]
Chan *et al.* 2020[23]	4.3 (20 mg if CrCl < 50) 2.0 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF) 1.4 (15 or 10 mg if CrCl > 50 or <50; J-ROCKET AF) 2.7 (10 mg if CrCl > 50)	4.5 (20 mg if CrCl < 50) 7.8 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF) 4.8 (15 or 10 mg if CrCl > 50 or <50; J-ROCKET AF) 4.5 (10 mg if CrCl < 50)	2.4 (20 mg if CrCl < 50) 1.3 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF) 0.7 (15 or 10 mg if CrCl > 50 or <50; J-ROCKET AF) 0.5 (10 mg if CrCl < 50)
Cheng *et al.* 2021[24]	0.9 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF or 15 or 10 mg if CrCl > 50 or <50; J-ROCKET AF) 2.8 (10 mg if CrCl > 50)	NR	NR

Continued

Table 1 *Continued*

Author	IS/SE[a] (rate per 100 PYs)	Mortality[a] (rate per 100 PYs)	Major bleeding[a] (rate per 100 PYs)
Fernandez *et al.* 2021[25]	1.1 (20 mg if CrCl < 50)	3.4 (20 mg if CrCl < 50)	2.3 (20 mg if CrCl < 50)
	0.5 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF)	2.3 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF)	0.8 (20 or 15 mg if CrCl > 50 or <50; ROCKET AF)
	0.4 (15 if CrCl > 50; J-ROCKET AF)	5.8 (15 if CrCl > 50; J-ROCKET AF)	1.3 (15 if CrCl > 50; J-ROCKET AF)

IS/SE, ischemic stroke/systemic embolism; PY, patient-year; TIA, transient ischemic attack.
[a]Crude annual incidence rate before adjustment.
[b]Not reporting annual incidence rate for patients treated with on-labelling, underdosing, and overdosing rivaroxaban individually.
[c]Only reporting annual incidence rate after adjustment.
[d]Only reporting overall incidence rate without annual adjustment.
[e]Not reporting annual incidence rate for rivaroxaban, dabigatran, or apixaban individually.
*ATRIA bleeding score.

study groups (4 points), comparability of groups (2 points), and ascertainment of exposure and outcomes (3 points), for a total score of 9 points. A score between 0 and 3 indicates a very high risk of bias, while a score between 4 and 6 indicates a high risk of bias, and a score between 7 and 9 indicates a low risk of bias.

Statistical analysis

All statistical analyses were performed by using the Review Manager 5.4 (The Cochrane Collaboration 2014, The Nordic Cochrane Center, Copenhagen, Denmark) and STATA version 14.0 (StataCorp, College Station, TX, USA). The logarithmic hazard ratio (HR) of the matched or adjusted effect estimates and the corresponding errors were pooled based on the use of inverse variance and random effect analysis. There were four studies only reporting event number and incidence rate of clinical outcomes among patients treated with rivaroxaban following different dosage criteria.[6–9] Therefore, the HR and 95% confidence interval (CI) was calculated using the number of events observed and the total number of person-years of observation in study groups reported in these studies. There were three studies reporting the HR regarding to the rivaroxaban following different dosage criteria vs. warfarin.[10–12] Therefore, the HR between the rivaroxaban following different dosage criteria was derived using the indirect comparison.[13] The degree of heterogeneity between studies was evaluated by using the I^2 index. Value of <25%, 25–50%, and ≥50% was defined as low, moderate, and high degrees of heterogeneity, respectively.[14] We used the funnel plot of the reported effect estimates to assess the risk of publication bias. A sensitivity analysis was conducted by removing one study at a time from the meta-analysis in order to determine the impact of the study on the overall results. A meta-regression analysis was performed to determine the factors that influenced the results. For all comparison in the present study, $P < 0.05$ was taken as statistically significant.

Eligibility and dosage adjustment of non-vitamin K antagonist oral anticoagulants

In the present study, patients treated with rivaroxaban were classified into 'rivaroxaban 10 mg daily if CrCl > 50 mL/min', 'J-ROCKET AF dosage criteria (15 mg daily if CrCl > 50 mL/min or 10 mg daily if CrCl < 50 mL/min)', 'ROCKET AF dosage criteria (20 mg daily if CrCl > 50 mL/min or 15 mg daily if CrCl < 50 mL/min)', and 'rivaroxaban 20 mg daily if CrCl < 50 mL/min' generally based on the dosage reduction criteria of pivotal rivaroxaban randomized trials.[1,2]

Of note, the Taiwan FDA approved rivaroxaban regimen following either the ROCKET AF or J-ROCKET AF dosage criteria for stroke prevention in AF patients.[1,2] The Japan FDA approved only rivaroxaban regimen following the J-ROCKET AF dosage criteria;[2] whole other countries/region outside Japan and Taiwan approved only rivaroxaban regimen following the ROCKET AF dosage criteria, for stroke prevention in AF patients.[1] Of note, patients receiving rivaroxaban 15 mg daily despite of CrCl > 50 mL/min outside Japan or Taiwan were classified to be eligible for the J-ROCKET AF dosage criteria, even though the J-ROCKET AF dosage criteria has not been approved in those countries; patients treated with off-label rivaroxaban 15 mg daily despite of CrCl < 50 mL/min in Japan were classified to be eligible for ROCKET AF dosage criteria, even though the ROCKET AF dosage criteria has not been approved in Japan.

Results

Study selection and characteristics

Figure 1 describes the study selection process. Overall, 160 articles were identified, and 124 were excluded after screening titles and abstracts. Subsequently, 20 studies were removed from the full-text review process [nine all non-vitamin K antagonist oral anticoagulants (NOACs) as a class, nine no outcome data, one no off-label dosing data, and one not off-label dose study]. Finally, 18 studies (with two studies added from author knowledge) involving 67 571 Asian and 54 882 non-Asian patients were included.[6–12,15–25] Among the 18 studies, 11 were conducted in Asia population (two in Taiwan, four in Japan, four in Korea, and one in China)[7–10,15–17,19,20,23,24] and 7 in non-Asia

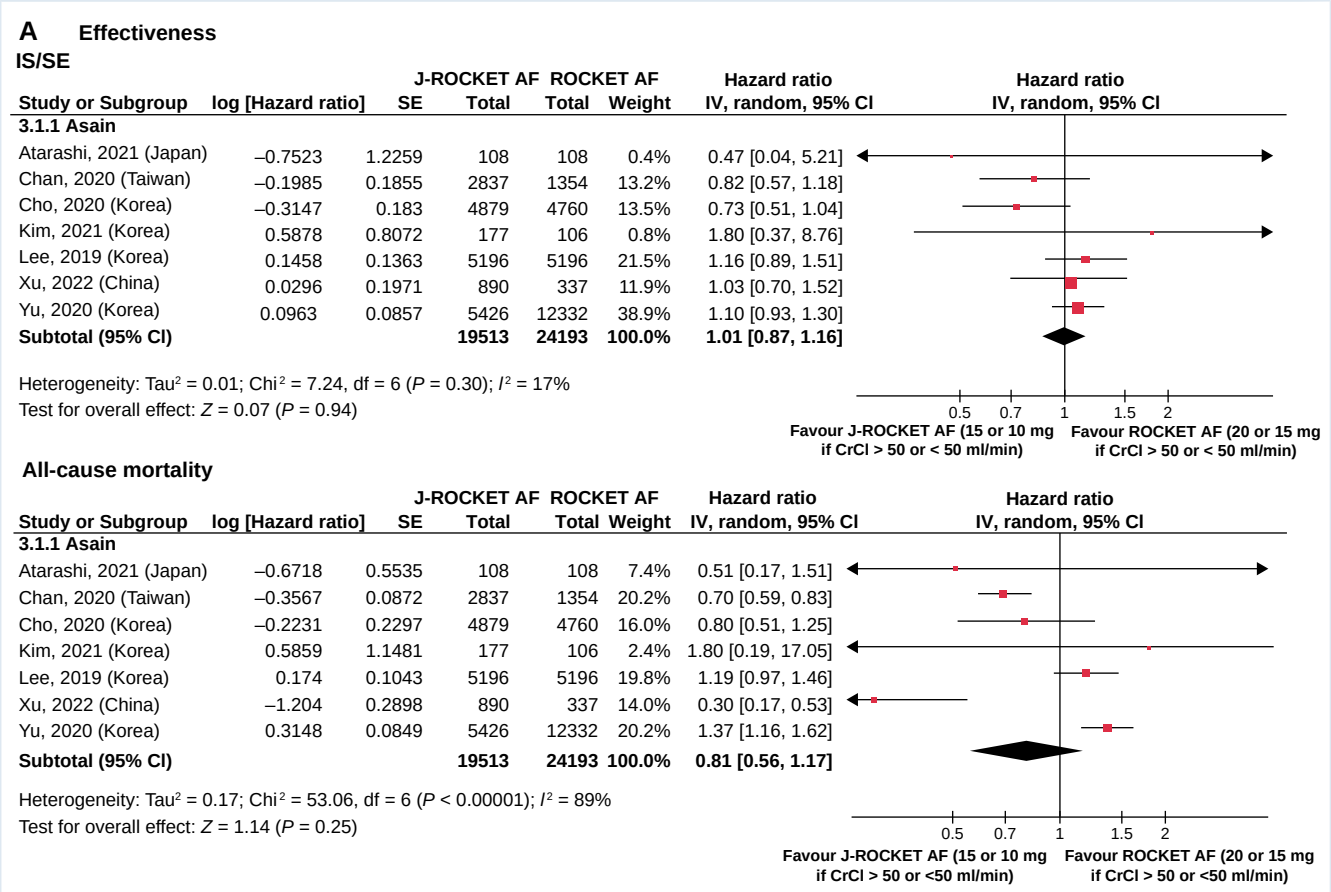


Figure 2 Comparison between the uses of rivaroxaban following J-ROCKET AF dosage criteria vs. that of ROCKET AF dosage criteria for effectiveness (*A*) and safety outcomes (*B*) in patients with NVAF in Asian population. CI, confidence interval; HR, hazard ratio; ICH, intracranial haemorrhage; GIB, gastrointestinal bleeding; NVAF, non-valvular atrial fibrillation.

population (Canada, USA, Europe, UK, and Spain).[6,11,12,18,21,22,25] *Table 1* summarizes the baseline characteristics of the enrolled studies. The comparisons between dosage criteria following J-ROCKET AF vs. ROCKET AF were assessed in 14 studies[6–8,10–12,16,18–23,25]; rivaroxaban 10 mg/day despite of CrCl > 50 mL/min vs. J-ROCKET AF/ROCKET AF dosage criteria in five studies[7,15,17,23,24]; and rivaroxaban 20 mg/day despite of CrCl < 50 mL/min vs. J-ROCKET AF/ROCKET AF dosage criteria in eight studies.[6,11,12,16,18,21,23,25] Most study cohorts were based on individual hospital-based electrical medical databases[8,9,12,18,20,22–24] and several prospective registries.[6,7,15,17,25] There were three studies using the Korea National Health Insurance Database with ~50 million enrolees.[10,16,19]

Risk of bias evaluation

Among the 18 included studies, there were two studies using a propensity score weighting method;[10,15] seven studies using propensity score matching methods;[7,8,17–21] and eight studies using multivariable logistic regression[6,11,12,16,22–25] to balance confounding factors between groups receiving rivaroxaban following different dosage criteria. There was one study reporting crude risk without adjusting for any baseline confounding factors.[9] A bias evaluation is summarized in Supplementary material online, *Table SI*. Overall, most studies reported a low risk of bias, while four studies had a risk of selection bias,[8,16,19,20] and six studies had a risk of performance bias.[6,7,10,15,17,25] The funnel plot visually shows the possibility of bias or small-study effects (see Supplementary material online, *Figures SI–SIII*). Majority of funnel plots was relatively symmetrical on visual inspection (see Supplementary material online, *Figures SI and SII*), with the exception of risk for thromboembolism (*P* for Egger's test = 0.018; *P* for Begg's test = 0.144) and major bleeding (*P* for Egger's test = 0.021; *P* for Begg's test = 0.026) of rivaroxaban 20 mg despite of CrCl < 50 mL/min (see Supplementary material online, *Figure SIII*). According to the Cochrane Handbook, publication bias was not required if <10 studies were included for each outcome. The funnel plots in this meta-analysis must therefore be interpreted with caution.

Comparison between dosage criteria following J-ROCKET AF vs. ROCKET AF in Asian and non-Asian populations

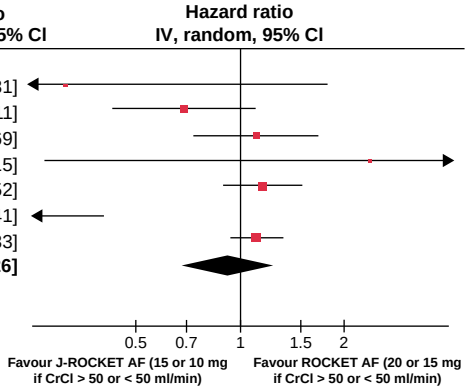
The use of rivaroxaban following J-ROCKET AF dosage criteria was associated with comparable risks of thromboembolism (HR, 1.01; 95% CI, 0.87–1.16; $n = 7$ with $I^2 = 17\%$) and all-cause mortality (HR, 0.81; 95% CI, 0.56–1.17; $n = 7$ with $I^2 = 89\%$) in the Asian population (*Figure 2*), whereas use of rivaroxaban following J-ROCKET AF dosage criteria was associated with a trend towards a higher risk of thromboembolism (HR, 1.26; 95% CI, 0.98–1.63; $n = 7$ with $I^2 = 32\%$) as well as a higher risk of all-cause mortality (HR, 1.30; 95% CI, 1.05–1.60; $n = 5$

B Safety

Major bleeding

Study or Subgroup	log [Hazard ratio]	SE	J-ROCKET AF Total	ROCKET AF Total	Weight	Hazard ratio IV, random, 95% CI
3.9.1 Asain						
Atarashi, 2021 (Japan)	–1.1571	0.8917	108	108	2.8%	0.31 [0.05, 1.81]
Chan, 2020 (Taiwan)	–0.3711	0.2413	2837	1354	17.9%	0.69 [0.43, 1.11]
Cho, 2020 (Korea)	0.1133	0.2114	4879	4760	19.9%	1.12 [0.74, 1.69]
Kim, 2021 (Korea)	0.8736	1.1113	177	106	1.9%	2.40 [0.27, 21.15]
Lee, 2019 (Korea)	0.1567	0.1323	5196	5196	25.5%	1.17 [0.90, 1.52]
Xu, 2022 (China)	–2.4079	0.7674	890	337	3.7%	0.09 [0.02, 0.41]
Yu, 2020 (Korea)	0.1133	0.0894	5426	12332	283%	1.12 [0.94, 1.33]
Subtotal (95% CI)			**19513**	**24193**	**100.0%**	**0.93 [0.68, 1.26]**

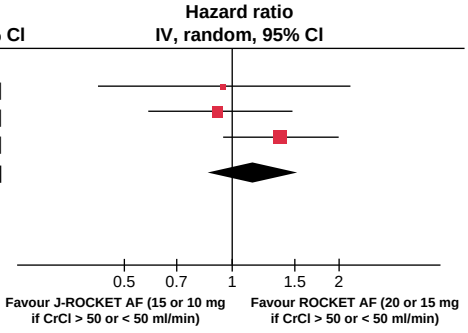
Heterogeneity: Tau^2 = 0.08; Chi^2 = 16.88, df = 6 (P < 0.00010); I^2 = 64%
Test for overall effect: Z = 0.49 (P = 0.62)



ICH

Study or Subgroup	log [Hazard ratio]	SE	J-ROCKET AF Total	ROCKET AF Total	Weight	Hazard ratio IV, random, 95% CI
3.4.1 Asain						
Chan, 2020 (Taiwan)	–0.0513	0.4160	2837	1354	11.1%	0.95 [0.42, 2.15]
Lee, 2019 (Korea)	–0.0843	0.2274	5196	5196	36.2%	0.92 [0.59, 1.44]
Yu, 2020 (Korea)	0.3148	0.1868	5426	12332	52.8%	1.37 [0.95, 1.98]
Subtotal (95% CI)			**13459**	**18882**	**100.0%**	**1.14 [0.87, 1.50]**

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.06, df = 2 (P = 0.36); I^2 = 3%
Test for overall effect: Z = 0.93 (P = 0.35)



GIB

Study or subgroup	log [Hazard ratio]	SE	J-ROCKET AF Total	ROCKET AF Total	Weight	Hazard ratio IV, random, 95% CI
3.5.1 Asain						
Chan, 2020 (Taiwan)	–0.5709	0.303	2837	1354	19.4%	0.57 [0.31, 1.02]
Kim, 2021 (Korea)	0.1804	1.2187	177	106	1.8%	1.20 [0.11, 13.05]
Lee, 2019 (Korea)	0.2744	0.1625	5196	5196	35.6%	1.32 [0.96, 1.81]
Yu, 2020 (Korea)	–0.0408	0.1125	5426	12332	43.1%	0.96 [0.77, 1.20]
Subtotal (95% CI)			**13636**	**18988**	**100.0%**	**0.97 [0.70, 1.35]**

Heterogeneity: Tau^2 = 0.05; Chi^2 = 6.55, df = 3 (P = 0.09); I^2 = 54%
Test for overall effect: Z = 0.17 (P = 0.87)

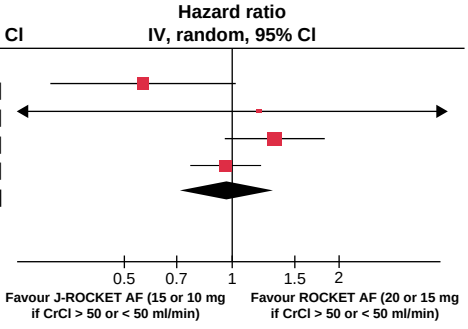


Figure 2 Continued

with I^2 = 51%) when compared with that of ROCKET AF dosage criteria in the non-Asian population (*Figure 3*). There were no differences in risks of major bleeding, ICH, and GIB between the uses of rivaroxaban following J-ROCKET AF vs. ROCKET AF dosage criteria either in the Asian or non-Asian population (*Figures 2* and *3*).

Comparison between rivaroxaban 10 mg daily if CrCl > 50 mL/min vs. J-ROCKET AF/ROCKET AF dosage criteria in Asian population

The use of rivaroxaban 10 mg daily despite of CrCl > 50 mL/min was associated with higher risk of thromboembolism (HR, 1.64; 95% CI, 1.28–2.11; n = 6 with I^2 = 49%) but lower risk of major bleeding (HR, 0.72; 95% CI, 0.57–0.90; n = 6 with I^2 = 0%), GIB (HR, 0.29; 95% CI, 0.10–0.83; n = 2 with I^2 = 0%), and any bleeding (HR, 0.70; 95% CI, 0.62–0.78; n = 4 with I^2 = 0%) when compared with use of rivaroxaban following J-ROCKET AF/ROCKET AF dosage criteria in Asian population. There was no difference in risks of all-cause mortality and ICH between the uses of rivaroxaban 10 mg daily despite of CrCl > 50 mL/min vs. rivaroxaban following eligible dosage criteria (*Figure 4*). There were no data available comparing the use of rivaroxaban 10 mg daily despite of CrCl > 50 mL/min vs. rivaroxaban following eligible dosage criteria in non-Asian population.

Comparison between rivaroxaban 20 mg daily if CrCl < 50 mL/min vs. J-ROCKET AF/ROCKET AF dosage criteria

The use of rivaroxaban 20 mg daily despite of CrCl < 50 mL/min was associated with higher risk of thromboembolism (HR, 1.32; 95% CI, 1.09–1.59; n = 9 with I^2 = 14%), all-cause mortality (HR, 1.33; 95%

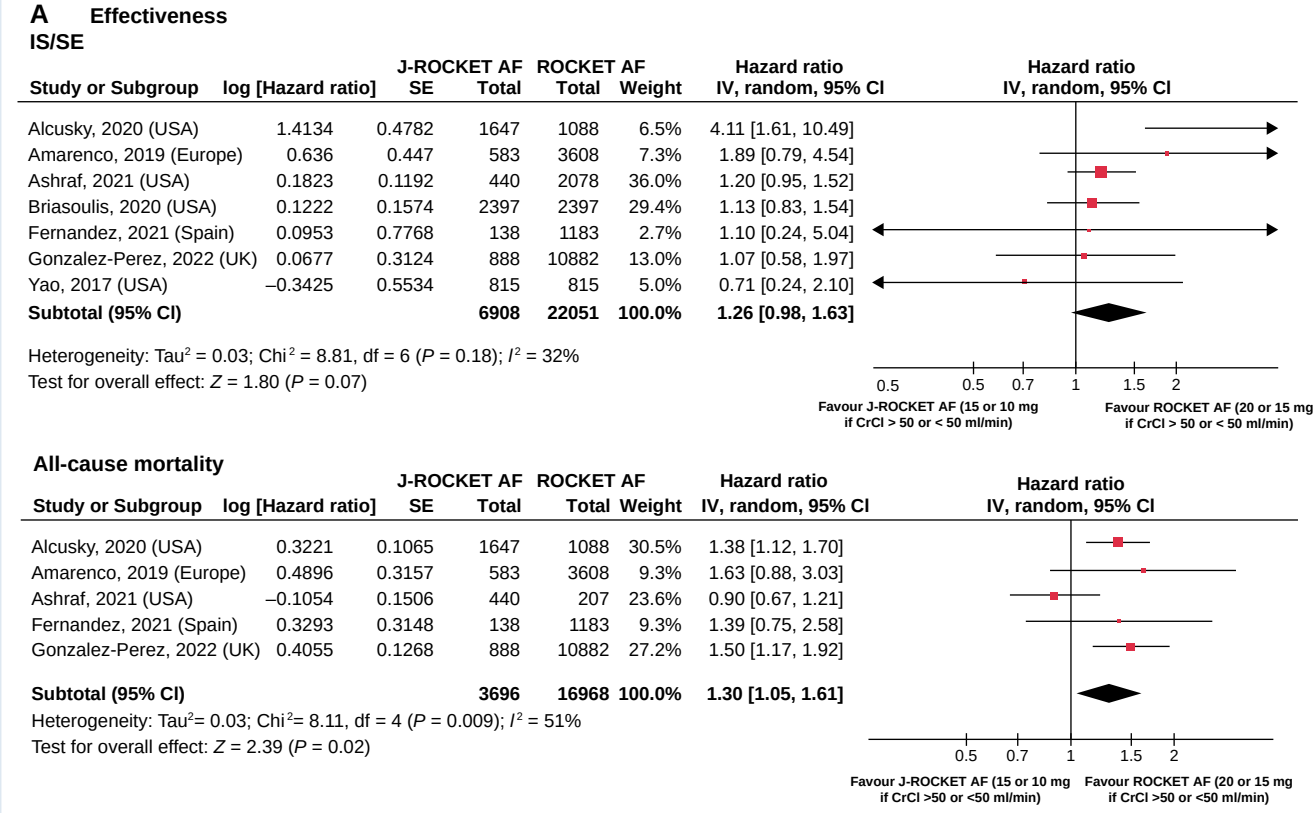


Figure 3 Comparison between the uses of rivaroxaban following J-ROCKET AF dosage criteria vs. that of ROCKET AF dosage criteria for effectiveness (*A*) and safety outcomes (*B*) in patients with NVAF in non-Asian population. The abbreviations as in *Figure 2*.

CI, 1.10–1.59; $n = 7$ with $I^2 = 52\%$), major bleeding (HR, 1.26; 95% CI, 1.03–1.54; $n = 7$ with $I^2 = 24\%$), and marginally higher risk of GIB (HR, 1.37; 95% CI, 1.00–1.89; $n = 4$ with $I^2 = 77\%$) when compared with use of rivaroxaban following J-ROCKET AF/ROCKET AF dosage criteria. There was no difference in risk of ICH between the uses of rivaroxaban 20 mg daily despite of CrCl < 50 mL/min vs. rivaroxaban following eligible dosage criteria (*Figure 5*).

Sensitivity analysis and meta-regression

Sensitivity analyses were conducted by sequentially removing a single study at one time (leave-one-out analysis). The pooled results were generally in line with the primary effectiveness and safety outcomes (see Supplementary material online, *Tables S2–S5*). Meta-regression analyses failed to detect any potential patient characteristics associated with the clinical outcomes ($P > 0.05$ for each variable; Supplementary material online, *Tables S6–S9*), with the exception of the year of publication ($P = 0.044$) and CHA_2DS_2-VASc score ($P = 0.023$) for the all-cause mortality in comparison between dosage criteria following J-ROCKET AF vs. ROCKET AF in Asians and the use of antiplatelet agent ($P = 0.036$) for the all-cause mortality in comparison between uses of rivaroxaban 20 mg daily despite of CrCl < 50 mL/min vs. J-ROCKET AF/ROCKET AF dosage criteria.

Discussion

This is the first meta-analysis to directly compare the effectiveness and safety of rivaroxaban following J-ROCKET AF vs. ROCKET AF dosage criteria among patients with NVAF in real-world clinical practice. Before this, only Taiwan has approved the use of rivaroxaban eligible for either J-ROCKET AF or ROCKET AF dosage criteria, which was enable for the direct comparison between J-ROCKET AF or ROCKET AF dosage criteria for stroke prevention in patients with NVAF,[23,26] and whether the finding from Taiwan can be applied to other countries/regions worldwide remained unknown. Our principal findings are as follows: (i) in the Asian population, use of rivaroxaban following J-ROCKET AF dosage criteria was associated with comparable effectiveness and safety outcomes when compared with that of ROCKET AF dosage criteria, whereas following the ROCKET AF dosage criteria remained a more favourable choice for the non-Asian population, which was associated with a trend towards a lower risk of thromboembolism and a significant lower risk of all-cause mortality but not a higher risk of major bleeding when compared with the J-ROCKET AF dosage criteria; (ii) use of rivaroxaban 10 mg daily despite of CrCl > 50 mL/min was associated with higher risk of thromboembolism but lower risk of major bleeding, GIB, and any bleeding when compared with that of J-ROCKET AF/ROCKET AF dosage criteria in Asian population; and (iii) use of rivaroxaban 20 mg daily despite of CrCl < 50 mL/min was associated with worse clinical outcomes when compared with use of rivaroxaban following eligible dosage criteria.

J-ROCKET AF vs. ROCKET AF dosage criteria in stroke prevention

Our present findings re-emphasize the importance to prescribe NOACs (non-vitamin K antagonist oral anticoagulant) at an 'on-label' dose for stroke prevention.[27–30] However, a debate about the dose

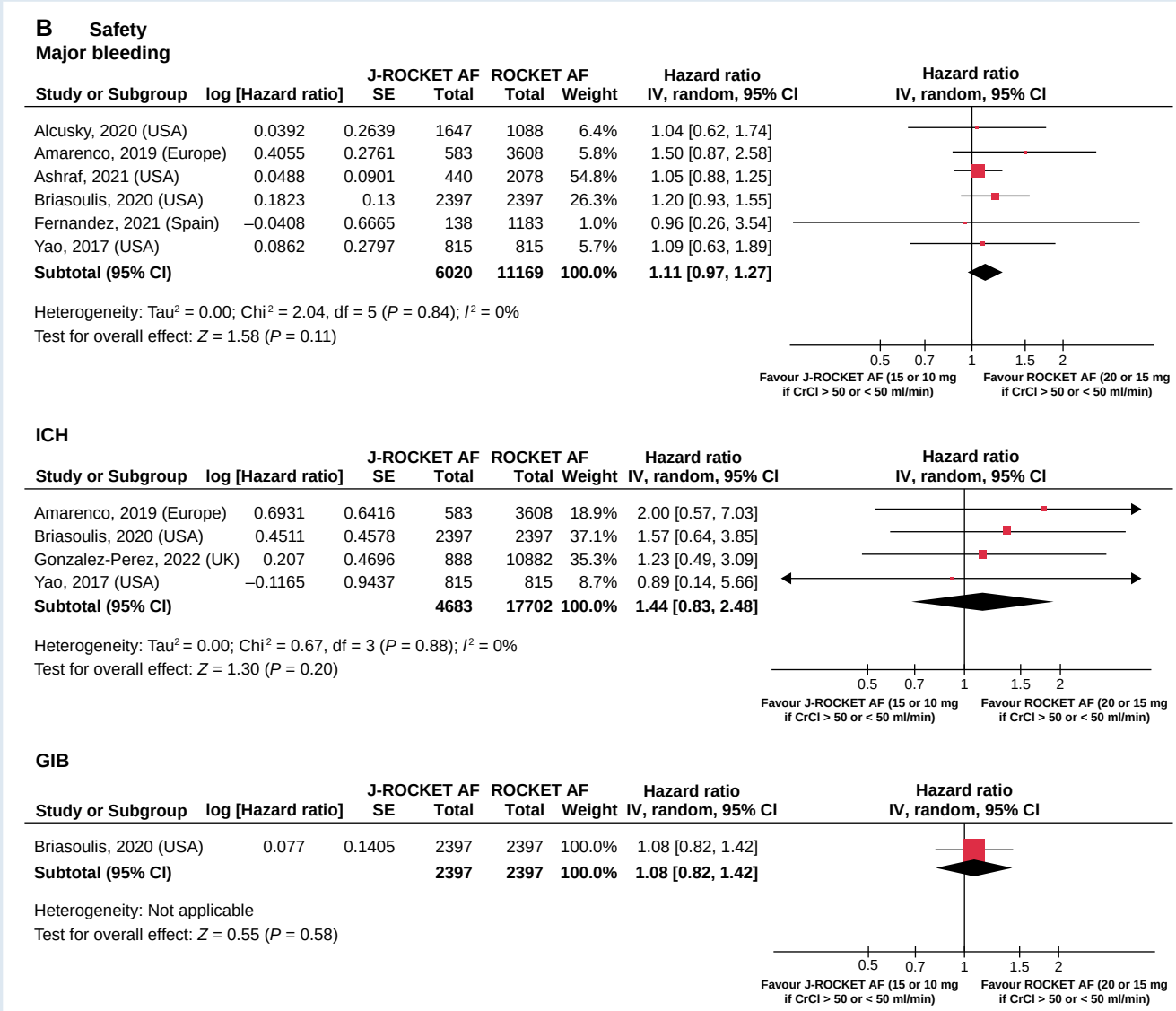


Figure 3 Continued

of rivaroxaban is that whether a lower dose regimen (15/10 mg daily) following the J-ROCKET AF dosage criteria, which was based on the unique pharmacokinetics in Japanese subjects showing a comparable rivaroxaban exposure when receiving the rivaroxaban 15/10 mg daily in contrast to the Caucasian subjects receiving the rivaroxaban 20/15 mg daily,[31] should be regarded as an 'on-label' dosage especially for Asian AF patients. Even though the J-ROCKET AF trial showed a comparable risk of thromboembolism and major bleeding than warfarin, compatible with the global ROCKET AF trial in patients with NVAF, the sample size of J-ROCKET AF trial was substantially smaller ($n = 1280$) than that of global ROCKET AF trial ($n = 14\,264$).[1,2] Furthermore, the target range of international normalized ratio in placebo group treated with warfarin in the J-ROCKET AF trial [International normalized ratio (INR) 1.6–2.6 for patients aged ≥70 years] was different from that of the ROCKET AF trial (INR 2.0–3.0 for all patients' age).

Age is a strong and independent risk factor for both stroke and bleeding in AF patients treated with rivaroxaban.[32] Many very elderly patients may have an indication for reduced dosing related to kidney function considering the labelling of rivaroxaban. It is, however, possible that some patients treated with a lower dose rivaroxaban were actually underdosed considering the labelling of the drug.[33] Indeed, previous analyses showed that age, high bleeding risk (HAS-BLED score ≥ 3), and impaired renal function are important drivers associated with inappropriate NOAC underdosing.[34] Previous studies also indicated that Asian AF patients had a higher risk of ICH compared to non-Asians treated with NOACs suggesting that Asians are more prone to bleeding.[35–38] Therefore, clinicians in Asia tend to prescribe a lower dose of NOACs for their patients in the daily practice.[39] Indeed, J-ROCKET dosage criteria is the only dosage regimen approved in Japan for stroke prevention in AF. Even in South Korea and China where J-ROCKET dosage criteria was not approved, use of rivaroxaban 15 mg rather than 20 mg daily accounted for more than 50% of the prescriptions.[20,40] Therefore, it is important to understand the safety and effectiveness of rivaroxaban following J-ROCKET AF dosage criteria compared to that of ROCKET AF. In the present meta-analysis, we show that the effectiveness and safety outcomes did not differ significantly between J-ROCKET AF and ROCKET AF dosage criteria in

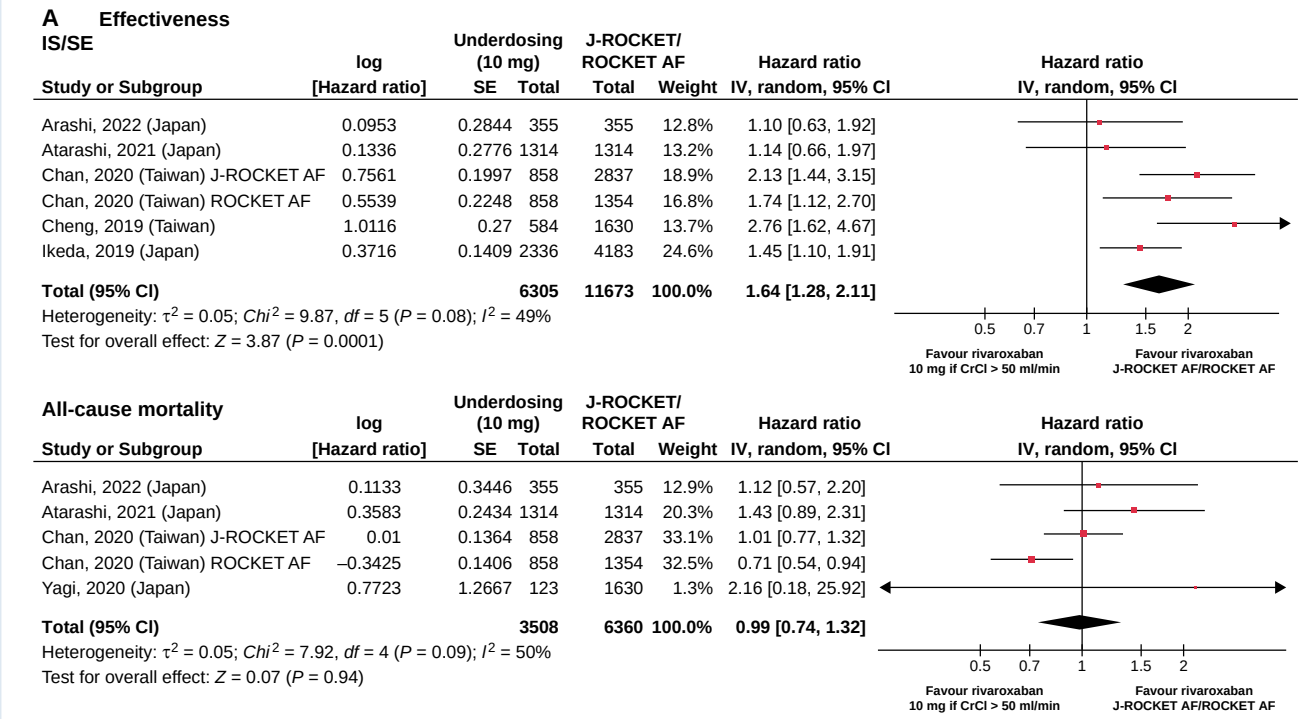


Figure 4 Comparison between uses of rivaroxaban 10 mg daily if creatinine clearance (CrCl) > 50 mL/min) vs. J-ROCKET AF/ROCKET AF dosage criteria for effectiveness (*A*) and safety outcomes (*B*) in patients with NVAF in Asian population. CrCl, creatinine clearance rate; other abbreviations as in *Figure 2*.

the Asian population. Our findings provided insights into the performance of rivaroxaban following J-ROCKET criteria suggesting that it may serve as an alternative to ROCKET AF criteria for Asian patients with NVAF, whereas that of ROCKET AF dosage criteria is still recommended in the non-Asian population, which was associated with a lower risk of thromboembolism and all-cause mortality but not a higher risk of major bleeding when compared with that of J-ROCKET AF dosage criteria.

Pharmacokinetics and pharmacodynamics analysis of rivaroxaban in Asians vs. non-Asians

In Thailand, the labelling dosage of rivaroxaban for patients with NVAF also follows the ROCKET AF dosage criteria. Although the median anti-FXa activity measured at the peak in patients with NVAF was significantly higher for the rivaroxaban dosage following the ROCKET AF than that of J-ROCKET AF, the median anti-FXa activity measured at the peak for the 20 mg/day reported in a Caucasian AF population (289 μg/L)[41] seems to be more comparable to that of the 15 mg/day (298 μg/L), rather than the 20 mg/day (364 μg/L), in Thai AF patients with preserved renal function.[42] Further studies show that a higher proportion of patients receiving the rivaroxaban 15/10 mg daily had anti-FXa activity measured at peak within the expected range than patients receiving the rivaroxaban 20/15 mg daily.[42,43] Of importance, one-third of patients receiving the rivaroxaban following the ROCKET AF in the present study had anti-FXa activity measured at peak that was higher than the expected range (>419 μg/L).[42,43] The above finding raised the concern that the J-ROCKET AF dosage recommendation may be more appropriate in the Thai population for stroke prevention. Conversely, one study in Taiwan showed that there were only ~30% of patients with the peak/trough levels of drug level achieved within the expected range in AF patients treated with rivaroxaban, with majorly (~75%) following the J-ROCKET AF dosage criteria.[44] Other studies also indicated that the pharmacokinetics of rivaroxaban were similar between healthy Chinese and Caucasian participants.[45,46] One recent systematic review investigated potential ethnic differences in the pharmacokinetic/pharmacodynamic characteristics of rivaroxaban between Asian and Caucasian populations, enrolling 24 studies with 10 on Asian adults, 11 on predominantly Caucasian adults, and 3 on Caucasian paediatrics.[47] The apparent clearance (CL/F) of rivaroxaban in Caucasian adults with NVAF (6.45–7.64 L/h) was ~31–43% higher than that in Asians (4.46–5.98 L/h) treated with 10–20 mg rivaroxaban every 24 h. Moreover, there was no obvious difference in CL/F among Japanese, Chinese, Thai, and Irani people. The relationship between exposure and response of rivaroxaban was comparable between Asians and Caucasians. The CL/F is significantly influenced by renal function, but no covariate was identified for the exposure–response relationship. In conclusion, a lower dose of rivaroxaban may be more suitable for Asians. Furthermore, previous study indicated that plasma monitoring of anti-FXa activity enables personalized and appropriate off-label underdosing in NVAF patients treated with rivaroxaban.[28,48]

Use of rivaroxaban 10 mg despite of CrCl > 50 mL/min for stroke prevention in Asian population

Our meta-analysis reveals that rivaroxaban 10 mg/day despite of preserved renal function was associated with a higher risk of thromboembolism but lower risk of most bleeding outcomes when compared with use of rivaroxaban following the J-ROCKET AF/ROCKET AF dosage criteria in Asian. Not surprisingly, bleeding events less common in

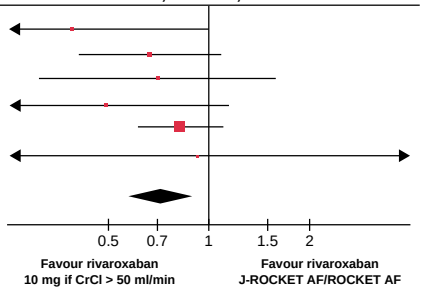
B Safety

Major bleeding

Study or Subgroup	log [Hazard ratio]	SE	Underdosing (10 mg) Total	J-ROCKET/ ROCKET AF Total	Weight	Hazard ratio IV, random, 95% CI
Arashi, 2022 (Japan)	–0.9416	0.4804	355	355	5.7%	0.39 [0.15, 1.00]
Atarashi, 2021 (Japan)	–0.409	0.2507	1314	1314	20.9%	0.66 [0.41, 1.09]
Chan, 2020 (Taiwan) J-ROCKET AF	–0.3567	0.4156	858	2837	7.6%	0.70 [0.31, 1.58]
Chan, 2020 (Taiwan) ROCKET AF	–0.7133	0.4323	858	1354	7.0%	0.49 [0.21, 1.14]
Ikeda, 2019 (Japan)	–0.1985	0.1509	2336	4183	57.8%	0.82 [0.61, 1.10]
Yagi, 2020 (Japan)	–0.0738	1.1679	123	500	1.0%	0.93 [0.09, 9.16]
Total (95% CI)			**5844**	**10543**	**100.0%**	**0.72 [0.57, 0.90]**

Heterogeneity: Tau^2 = 0.00; Chi^2 = 3.32, df = 5 (P = 0.65); I^2 = 0%

Test for overall effect: Z = 2.89 (P = 0.004)

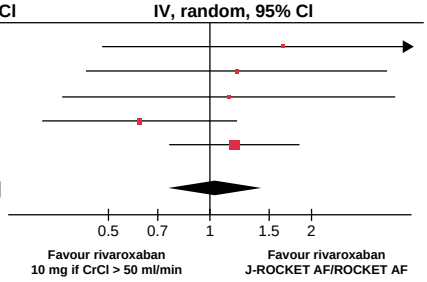


ICH

Study or Subgroup	log [Hazard ratio]	SE	Underdosing (10 mg) Total	J-ROCKET/ ROCKET AF Total	Weight	Hazard ratio IV, random, 95% CI
Arashi, 2022 (Japan)	0.5008	0.63	355	355	6.7%	1.65 [0.48, 5.67]
Chan, 2020 (Taiwan) J-ROCKET AF	0.1823	0.5236	858	2837	9.7%	1.20 [0.43, 3.35]
Chan, 2020 (Taiwan) ROCKET AF	0.1284	0.5783	858	1354	7.9%	1.14 [0.37, 3.53]
Cheng, 2019 (Taiwan)	–0.478	0.3375	584	1630	23.2%	0.62 [0.32, 1.20]
Ikeda, 2019 (Japan)	0.1655	0.2245	2336	4183	52.5%	1.18 [0.76, 1.83]
Total (95% CI)			**4991**	**10359**	**100.0%**	**1.04 [0.75, 1.43]**

Heterogeneity: τ^2 = 0.00; Chi^2 = 3.30, df = 4 (P = 0.51); I^2 = 0%

Test for overall effect: Z = 0.23 (P = 0.82)

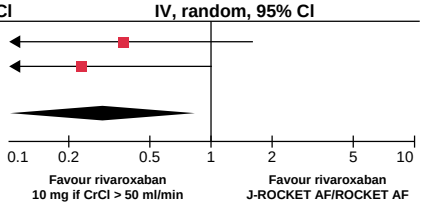


GIB

Study or Subgroup	log [Hazard ratio]	SE	Underdosing (10 mg) Total	J-ROCKET/ ROCKET AF Total	Weight	Hazard ratio IV, random, 95% CI
Chan, 2020 (Taiwan) J-ROCKET AF	–0.9889	0.7472	858	2837	50.6%	0.37 [0.09, 1.61]
Chan, 2020 (Taiwan) ROCKET AF	–1.474	0.7564	858	1354	49.4%	0.23 [0.05, 1.01]
Total (95% CI)			**1716**	**4191**	**100.0%**	**0.29 [0.10, 0.83]**

Heterogeneity: τ^2 = 0.00; Chi^2 = 0.21, df = 1 (P = 0.65); I^2 = 0%

Test for overall effect: Z = 2.31 (P = 0.02)



Any bleeding

Study or Subgroup	log [Hazard ratio]	SE	Underdosing (10 mg) Total	J-ROCKET/ ROCKET AF Total	Weight	Hazard ratio IV, random, 95% CI
Arashi, 2022 (Japan)	–0.2744	0.165	355	355	11.6%	0.76 [0.55, 1.05]
Atarashi, 2021 (Japan)	–0.289	0.1038	1314	1314	29.4%	0.74 [0.61, 0.91]
Ikeda, 2019 (Japan)	–0.4155	0.0748	2336	4183	56.6%	0.66 [0.57, 0.76]
Yagi, 2020 (Japan)	–0.2998	0.3672	123	500	2.3%	0.74 [0.36, 1.52]
Total (95% CI)			**4128**	**6352**	**100.0%**	**0.70 [0.62, 0.78]**

Heterogeneity: τ^2 = 0.00; Chi^2 = 1.20, df = 3 (P = 0.75); I^2 = 0%

Test for overall effect: Z = 6.43 (P < 0.00001)

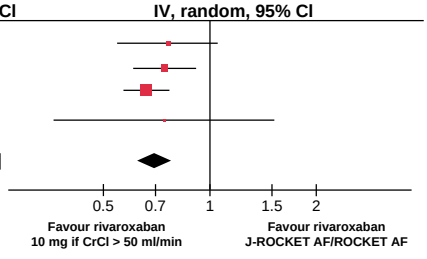


Figure 4 Continued

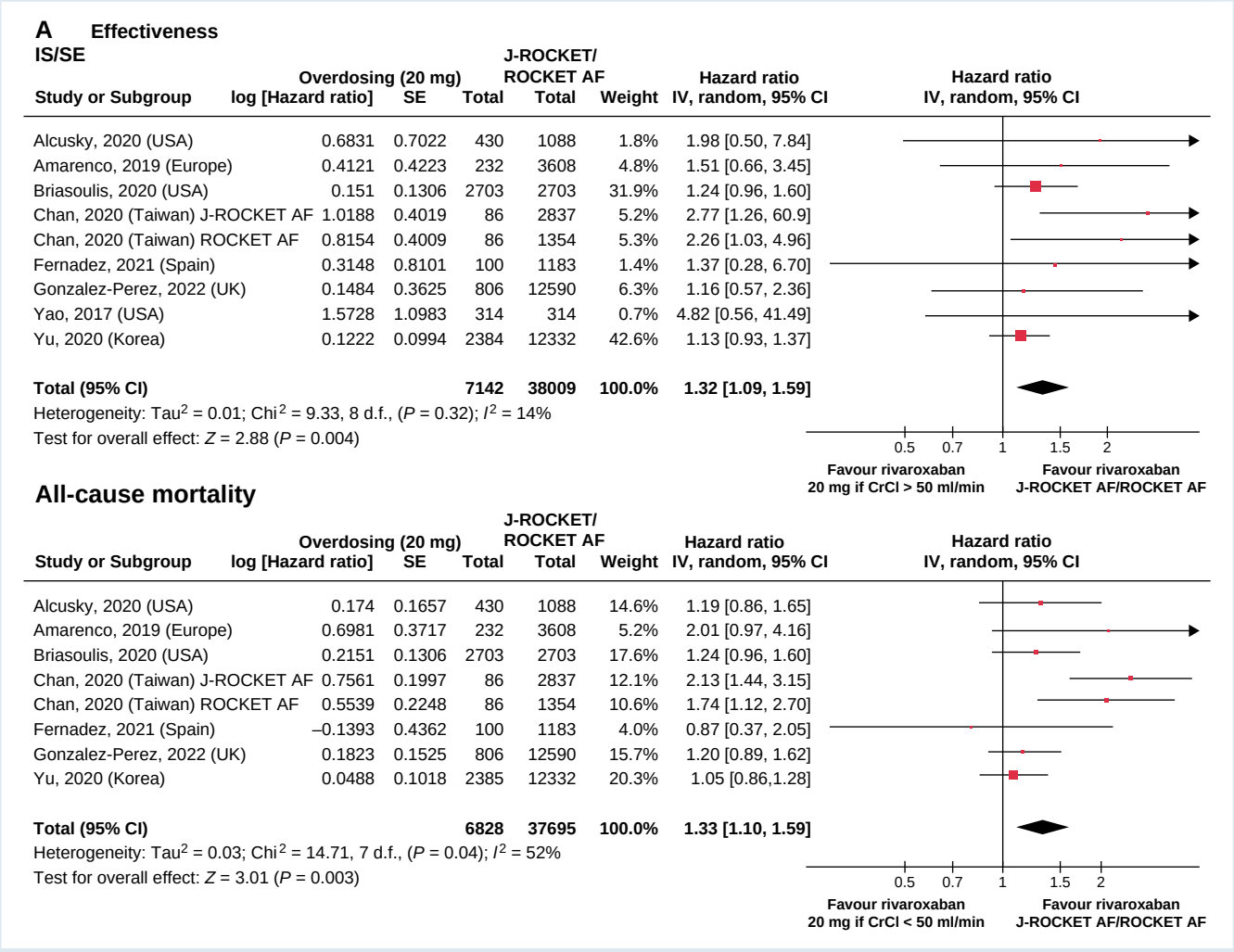


Figure 5 Comparison between uses of rivaroxaban 20 mg daily if CrCl < 50 mL/min vs. J-ROCKET AF/ROCKET AF dosage criteria for effectiveness (*A*) and safety outcomes (*B*) in patients with NVAF. The abbreviations as in *Figure* 2.

the expense of exceeding risk of ischaemic stroke/systemic embolism with underdosed rivaroxaban, though with the balance between benefit and harm, are unclear. A *post hoc* analysis of ENGAGE AF-TIMI 48 trial showed that several net clinical outcomes were comparable or even reduced with low-dose edoxaban 30/15 mg daily vs. standard-dose edoxaban 60/30 mg daily.[49] The ELDERCARE-AF trial also showed that edoxaban 15 mg once daily was superior to placebo in preventing stroke/systemic embolism and did not result in a significantly higher risk of major bleeding than placebo in very elderly Japanese patients (>80 years old) with NVAF who were not appropriate candidates for standard doses of OACs.[50] The *post hoc* analysis of AFIRE trial showed that in AF patients with stable coronary artery disease and preserved renal function, use of (underdosed) rivaroxaban 10 mg daily was associated with a comparable risk of thromboembolism but a lower risk of bleeding events than rivaroxaban 15 mg daily following the J-ROCKET AF dosage criteria, whereas a significant decrease in the incidence of the primary safety endpoint in the underdosed group was observed in patients on combination therapy with rivaroxaban and an antiplatelet agent but not in those on monotherapy with rivaroxaban.[17] It is noted that above analysis specifically focused on the Asian population, and the rivaroxaban 10 mg dose was never approved for AF stroke prevention even in the presence of a reduced CrCl < 50 mL/min in Western countries.

Use of rivaroxaban 20 mg despite of CrCl < 50 mL/min in stroke prevention

In our analysis, the increase in risk of thromboembolism and all-cause mortality with the use of rivaroxaban 20 mg/day were unanticipated and are difficult to explain on the basis of the biologic effects of antithrombotic therapy. Interestingly, the AFIRE trial also showed that rivaroxaban monotherapy (following the J-ROCKET AF dosage criteria) resulted in lower risks of bleeding events as well as the ischaemic events and all-cause death when compared with rivaroxaban plus one antiplatelet therapy in AF patients with stable coronary artery disease.[51] Nevertheless, our present analysis may be biased by the unmeasured confounding that could not be fully accounted for, especially for the analysis of the overdosed rivaroxaban subgroup given that the number of participants receiving this dosage was very limited.

Comparison with recent systematic reviews or meta-analyses on off-label dosing of NOACs

When we searched PubMed for other relevant systematic reviews or meta-analyses, we found several well-written systematic reviews that

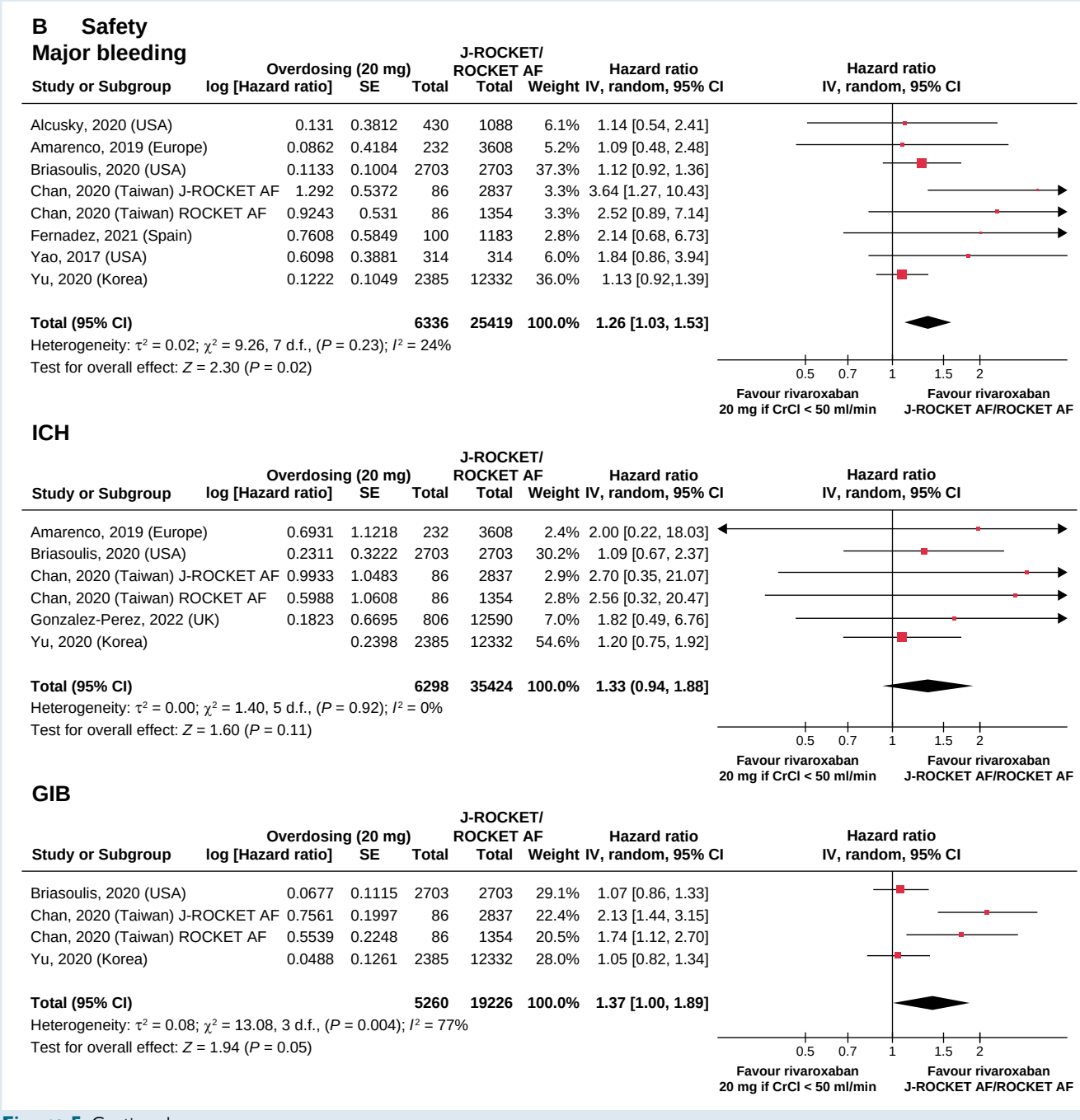


Figure 5 Continued

provided a comprehensive summary of recent evidence on off-label dosing of NOACs.[52–54] Although those systematic reviews in general showed that, compared with on-label dosing, off-label underdosing of NOACs increased the risk of thromboembolic events but did not decrease the risk of bleeding, and limited data for off-label overdosing showed higher risks of thromboembolic and bleeding, inconsistencies remain in these results.[52–54] These differences could be attributed to population characteristics (e.g. mean age and ethnicity), small sample sizes, distinct definitions of underdosing and overdosing, and other variables. Furthermore, previous meta-analyses did not mainly focus on rivaroxaban and have classified (if they have performed subgroup analysis of specific NOAC) the underdosing of rivaroxaban (10 mg daily if CrCl > 50 mL/min) and rivaroxaban (15/10 mg eligible for the J-ROCKET AF dosage criteria) as the 'off-label' underdosing of rivaroxaban, and those studies did not separate the Asian and non-Asian populations specifically. These meta-analyses have led to the conclusion that rivaroxaban (20/15 mg) labelling to the ROCKET AF dosage criteria is recommended for stroke prevention in AF patients. However, the issue regarding the rivaroxaban 15/10 mg eligible for the J-ROCKET AF dosage criteria or an even lower dosing of rivaroxaban (e.g. 10 mg if CrCl > 50 mL/min) has not been fully addressed. Also, several recently published studies investigating a lower dosing of rivaroxaban have not been included in these meta-analyses yet.[7–9,11,12,17,20] Considering the high prevalence of underdosed rivaroxaban prescriptions in the Asian

population[3] and the fact that some studies (in China, Japan, Taiwan, and Thailand) have proposed the use of a lower dosage of rivaroxaban (e.g. rivaroxaban 15/10 mg eligible for the J-ROCKET AF dosage criteria) for AF stroke prevention from the clinical or pharmacokinetic/pharmacodynamic aspect,[2,20,23,31,47] it is necessary to perform a more comprehensive review and analysis focused on the issue.

Study limitations

This study had several limitations. First, the present meta-analysis was performed at a study level rather than a patient level because the individual patient data from each enrolled study were not available. A major study limitation embedded within the meta-analysis is that no randomized controlled studies have been analysed, and therefore, confounders may impact on the results and conclusion. For a direct comparison, a dedicated trial that randomized participants after stratification for each dose strategy of rivaroxaban would be required. However, such prospective and randomized studies for the treatment of under or overdosing rivaroxaban may have the possibility of causing the ethical problem. Secondly, there was a moderate to significant heterogeneity ($I^2 > 25\%$) in results reporting the risk of thromboembolism and bleeding regarding to the rivaroxaban 20 mg daily despite of CrCl < 50 mL/min vs. use of rivaroxaban following J-ROCKET AF/ROCKET AF dosage criteria. Thirdly, we did not perform further subgroup analysis in Asian and non-Asian populations for the comparisons between rivaroxaban 10 mg/day despite of CrCl > 50 mL/min vs. J-ROCKET AF/ROCKET AF dosage criteria and rivaroxaban 20 mg/day vs. J-ROCKET AF/ROCKET AF dosage criteria, because all the comparisons between underdosed rivaroxaban 10 mg/day vs. eligible dosage criteria were obtained from Japan and Taiwan, whereas the majority of the comparisons between rivaroxaban 20 mg daily despite of CrCl < 50 mL/min vs. eligible dosage criteria was obtained from the non-Asian population. Fourthly, the majority of studies included in the meta-analysis did not report clinical outcomes of rivaroxaban stratified by specific subgroup of interest (e.g. age). Consequently, based on their findings, we are unable to conduct any additional subgroup analysis on this topic. Finally, the cause of patients receiving a very low-dose rivaroxaban despite meeting criteria for eligible dosage criteria may be due to the perception of higher bleeding risk that was not reflected in the baseline covariate by each primary care physician. Similarly, patients may receive a regular or over dosage rivaroxaban if the primary care physician deemed their bleeding risk to be low. Although we adopted the studies reporting adjusted HRs by using either propensity score weighting or matching, or multivariate Cox regression with several baseline variables, residual confounding with unmeasured variables and selective prescribing behaviour could not be excluded in the present meta-analysis due to the nature of real-world data.

Conclusions

Rivaroxaban dosing regimen following J-ROCKET criteria may serve as an alternative to ROCKET AF criteria for the Asian population with NVAF, whereas the dosing regimen following ROCKET AF criteria was more favourable for the non-Asian population. The use of rivaroxaban 10 mg despite of CrCl > 50 mL/min was associated with a higher risk of thromboembolism but a lower risk of major bleeding, while use of rivaroxaban 20 mg despite of CrCl < 50 mL/min was associated with worse outcome in most clinical events, including thromboembolism, bleeding, and all-cause death. Appropriate dose selection based on the results of the pivotal trial is indeed a key element in AF patients treated with NOAC as stressed in the practical guidelines on NOACs.[27–30]

Supplementary material

Supplementary material is available at *Europace* online.

Authors' contributions

Study concept and design: Y.-H.C., T.-F.C. Acquisition of data: Y.-H.C., C.-Y.C. Analysis and interpretation of data: Y.-H.C., C.-Y.C., S.-W.C., T.-F.C. Drafting of the manuscript: Y.-H.C., T.-F.C., G.Y.H.L. Critical revision of the manuscript for important intellectual content: G.Y.H.L. Statistical analysis: Y.-H.C., C.-Y.C. Study supervision: T.-F.C., G.Y.H.L.

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Conflict of interest: None declared.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article or its supplementary materials.

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