Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Safety and efficacy of direct oral anticoagulants over warfarin in Japanese patients with acute venous thromboembolism: A meta-analysis

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ARTICLE INFO

Article history:
Received 21 April 2016
Received in revised form 17 June 2016
Accepted 6 July 2016
Available online xxx

Keywords:
Direct oral anticoagulants
Venous thromboembolism
Japanese
Meta-analysis

ABSTRACT

Background: Direct oral anticoagulants (DOACs) have been developed as alternatives to conventional therapy with warfarin for the treatment of acute venous thromboembolism (VTE) events. The safety and efficacy of DOACs in Japanese patients with acute VTE has been investigated in small trials or subgroups from global randomized controlled trials (RCTs).

Methods and Results: We conducted a systematic review and meta-analysis of RCTs, to compare the safety and efficacy of DOACs to those of conventional therapy in Japanese patients with acute VTE. Published research was systematically searched for RCTs that compared DOAC to conventional therapy in Japanese patients with acute VTE. Random-effects models were used to pool safety and efficacy data across RCTs. Three studies, including 386 patients, were identified. Patients randomized to DOAC had a decreased risk for all bleeding [risk ratio (RR) 0.69, 95% confidential interval (CI) 0.50–0.95], without any significant differences in recurrent VTE (RR 0.84, 95% CI 0.29–2.43) and recurrent VTE/all-cause death (RR 0.60, 95% CI 0.23–1.56).

Conclusion: DOACs offer clinical benefit over conventional therapy in Japanese patients with acute VTE, showing a significant difference in their bleeding profile.

Introduction

Until recently, warfarin was the standard oral anticoagulant in the treatment and prevention of recurrent venous thromboembolism (VTE) events in patients with acute VTE. More recently, the direct oral anticoagulants (DOACs) have been introduced as alternatives to warfarin.

The DOACs are categorized on the basis of their targets, as direct thrombin (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Several large phase III randomized controlled trials (RCTs), the Dabigatran versus warfarin in the treatment of acute venous thromboembolism (RE-COVER) trial [1], Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis (RE-COVER II) trial [2], the Oral rivaroxaban for the treatment of symptomatic pulmonary embolism (EINSTEIN-PE) trial [3], the Oral rivaroxaban for symptomatic venous thromboembolism (EINSTEIN-DVT) trial [4], the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) [5] trial, the Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism (Hokusai-VTE) trial [6], have examined the use of DOACs.

Although these trials showed that those DOACs are at least as safe and effective compared with conventional therapy with warfarin, their outcomes in Japanese population remain unclear. We therefore performed a systematic review and meta-analysis to examine the safety and efficacy of DOACs compared to conventional therapy in the treatment and prevention of recurrent VTE in Japanese patients with acute VTE.

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http://dx.doi.org/10.1016/j.jjcc.2016.07.007
0914-5087/

Methods

Search strategies

MEDLINE was searched for abstract and papers, and the following search terms were used (oral anticoagulants OR oral thrombin inhibitors OR oral factor Xa OR dabigatran OR rivaroxaban OR apixaban OR edoxaban) AND (venous thromboembolism OR pulmonary embolism OR deep vein thrombosis) AND Japanese. The electronic search was restricted to peer-reviewed journals published between 1 January 2006 and 31 March 2016. Clinical trial databases and relevant reviews were hand searched for potentially relevant studies not identified in our electronic database search.

Study selection and outcomes

The PRISMA statement for reporting systematic reviews and meta-analyses of RCTs [7] was used for the method of this study. Criteria for selection of trials for inclusion were 1) RCTs, 2) randomized subjects to conventional therapy with warfarin or to DOAC, and 3) included in Japanese patients. Conference abstracts and presentations were excluded, because their results may not be final, and such publications undergo more limited peer review. The main safety outcome of interest was all bleeding. The main efficacy outcome of interest was recurrent VTE. Other safety and efficacy outcomes were major bleeding/clinically relevant non-major (CRNM) bleeding and recurrent VTE/all-cause death.

Data extraction

Data were extracted by two reviewers independently and disagreements were resolved by consensus or, if necessary, by a third party. Data extracted from each RCT included patient- and study-level characteristics as well as outcomes. The characteristics of the patients were compared between studies, including: age, gender distribution, body weight, renal impairment, a history of VTE, and international normalized ratio (INR) level (Table 1).

Quality assessment

Quality assessment was performed using the Cochrane Collaboration's risk of bias tool [8].

Statistical analysis

Analyses were done using Review Manager 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Summary estimates were calculated as risk ratio (RR) using the random effects model based on DerSimonian and Laird's meta-analytic statistical method [9]. The random effects model was chosen in view of the significant methodological heterogeneity seen between the different studies. For meta-analyses, Cochran's χ^2 test and the I^2 statistic were quantified [8,10]. Cochran's χ^2 test assesses whether the observed differences in results may be due to chance alone, and a low p-value suggests the presence of significant statistical heterogeneity. The I^2 statistic is an alternative test that provides a measure of the inconsistency of the studies' results. It describes the percentage of total variation across the studies that is due to statistical heterogeneity rather than chance [8]. Although it is difficult to give thresholds for the significance of the I^2 statistic, I^2 was also ascertained, where I^2 represents an estimate of the degree of inconsistency among studies with scores of 25, 50, and 75% representing, respectively, low, moderate, or high inconsistency [10]. In all analyses, $p < 0.05$ was considered

Table 1
Baseline characteristics of RCTs.

Characteristics	Trial						
	AMPLIFY-J		Hokusai-VTE (Japanese population)		J-EINSTEIN DVT and PE		
	Apixaban	UFH/Warfarin	Edoxaban†	UFH/Warfarin	Rivaroxaban 10 mg bid/ 15 mg od	Rivaroxaban 15 mg bid/ 15 mg od	UFH/warfarin
Randomized N (DVT/PE)	40 (22/18)	40 (22/18)	106 (70/36)	103 (64/39)	23 (23/0)	55 (25/30)	19 (12/7)
Age (years) Mean ± SD	64.3 ± 13.4	66.1 ± 17.7	63.5 ± 14.6	65.8 ± 15.6	65.0 ± 9.9	68.8 ± 12.2	63.4 ± 18.3
Male *N* (%)	22 (55.0)	17 (42.5)	54 (50.9)	50 (48.5)	16 (69.6)	25 (45.5)	10 (52.6)
BW (kg) Mean ± SD	64.6 ± 12.9	58.1 ± 12.2	64.0 ± 12.6	63.1 ± 13.5			
BW ≤ 60 kg or <70 kg *N* (%)			BW ≤60 kg 46 (43.4)	42 (40.8)	BW <70 kg 15 (65.2)	41 (74.5)	15 (78.9)
Renal impairment *N* (%)	CrCL < 80 mL/min 20 (50.0)	CrCL < 80 mL/min 26 (65.0)	CrCL 30–50 mL/min 18 (17.0)	CrCL 30–50 mL/min 15 (14.7)	CrCL < 80 mL/min 9 (39.1)	CrCL < 80 mL/min 36 (65.5)	CrCL < 80 mL/min 11 (57.9)
Previous VTE *N* (%)	6 (15)	4 (10)			0	8 (14.5)	1 (5.3)
Median TTR (%)††		70.1		62.1			80.3
Mean follow up (days)	163.2	162.2	355	355	191.8	196.6	199.8
Dose	10 mg bid for 7 days, followed by 5 mg bid		60 mg (30 mg*) od		15 mg bid for 3 weeks, followed by 15 mg od		
Dosage adjustment	None		Weight ≤60 kg CrCL; 30–50 mL/min p-glycoprotein (p-gp) inhibitor		None		

RCT, randomized controlled trial; SD, standard deviation; BW, Body weight; CrCL, creatinine clearance; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; INR, international normalized ratio; UFH, unfractionated heparin; TTR, time in therapeutic range; bid, twice daily; od, once daily.
* Dosage adjustment.
† All patients received initial therapy with unfractionated heparin for at least 5 days.
†† TTR for INR control 1.5–2.5 in AMPLIFY-J and J-EINSTEIN DVT and PE trials, and 2.0–3.0 in Hokusai-VTE trial.

Please cite this article in press as: Senoo K, et al. Safety and efficacy of direct oral anticoagulants over warfarin in Japanese patients with acute venous thromboembolism: A meta-analysis. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2016.07.007