Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

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

Original article

Efficacy and safety of rivaroxaban in extreme elderly patients with atrial fibrillation: Analysis of the Shikoku Rivaroxaban Registry Trial (SRRT)

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ARTICLE INFO

Article history:
Received 23 May 2017
Received in revised form 8 August 2017
Accepted 23 August 2017
Available online xxx

Keywords:
Rivaroxaban
Anticoagulants
Extreme elderly
Atrial fibrillation

ABSTRACT

Background: The Shikoku Rivaroxaban Registry Trial (SRRT) is a retrospective survey of the use of rivaroxaban for stroke prevention in elderly patients in Shikoku, Japan.
Methods: The SRRT enrolled 1339 patients from 8 hospitals. Patients were divided into two groups according to their age, the extreme elderly group (453 patients aged ≧80 years) and the control group (886 patients aged <80 years).
Results: In the extreme elderly group, 41.5% of the patients had low body weight (<50 kg) and 65.1% had abnormal renal function (creatinine clearance <50 ml/min). The mean $CHADS_2$, CHA_2DS_2-VASc, and HAS BLED scores were 2.7, 4.4, and 2.3, respectively. There were 333 (73.5%) patients who met the dosing criteria, and of these patients, 81.2% received rivaroxaban 10 mg daily. Thromboembolic events occurred in 4 patients (0.94%/person year) and intracranial hemorrhage occurred in 4 patients (0.89%/person year). The incidence of these events was not significantly different from the control group. In addition, all patients with cerebral infarction had been treated with a smaller dose of rivaroxaban than recommended by the dosing criteria, suggesting that dosing criteria should be adhered to.
Conclusion: These results suggest that rivaroxaban is effective and safe in extreme elderly patients with atrial fibrillation.

Introduction

Atrial fibrillation (AF) is a global healthcare problem, currently affecting 2.5% of the population worldwide, its prevalence steeply increases with age [1], ranging from 9% in patients aged 76–85 years to >10% in those aged over 85 years. Currently, four types of direct oral anticoagulants (DOACs) are available in Japan. Rivaroxaban 20 mg once daily (o.d.) is used for the prevention of stroke and systemic embolism in patients with non-valvular AF in the global ROCKET AF trial. In Japan, however, old Japanese patients (age >70 years) receiving anticoagulant therapy may require lower therapeutic ranges than Westerners [international normalized ratio (INR) target level of 1.6–2.6]. The risk of intracranial

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http://dx.doi.org/10.1016/j.jjcc.2017.08.005
0914-5087/

hemorrhage rose as INR values exceeded 2.5 in Japanese [2]. For this reason, a reduced dose of 15 mg o.d. was used in the J-ROCKET AF trial, a separate trial to the ROCKET AF trial, and the results of the former study demonstrated the efficacy and safety of a lower dose of rivaroxaban, i.e. Japan-specific rivaroxaban dose. Recently, the results of the XANTUS [3] and XAPASS studies [4] have been reported; these are real-world prospective, observational studies of patients with AF treated with rivaroxaban for stroke prevention. However, there have been few studies that focused on the efficacy and safety of this drug in extreme elderly patients. In this study, we examined the efficacy and safety of rivaroxaban in extreme elderly patients aged ≧80 years in the Shikoku Rivaroxaban Registry Trial (SRRT).

Studied patients and methods

SRRT was a retrospective study that enrolled 1339 patients with non-valvular AF treated with rivaroxaban and recruited from 8 hospitals in Shikoku, Japan from April 18, 2012 to May 31, 2015. Among these patients, 453 (33.8%) were extreme elderly aged ≧80 years (the extreme elderly group), and 886 patients (66.2%) were under the age of 80 years (the control group). AFs were classified into paroxysmal or persistent. The data collected were age, sex, weight, dose of rivaroxaban, creatinine clearance (CrCl; calculated using the formula of Cockcroft–Gault), $CHADS_2$ score, CHA_2DS_2-VASc score, HAS-BLED score, duration of treatment, and other antithrombotic drugs used before rivaroxaban treatment.

Adverse events (cerebral infarction, systemic embolism, myocardial infarction, intracranial hemorrhage, and other bleeding events) were recorded. The volume of intracranial bleeding (hematoma of intracranial hemorrhage) was evaluated on computed tomography imaging with a 5 mm thick slice using ABC/2 method [5]. The modified Rankin Scale (mRS) was used to evaluate degree of disability at discharge [6].

Statistical analysis and ethical consideration

Values are expressed as mean ± standard deviation. For the comparison between two independent groups, the χ^2 test and Mann–Whitney *U* test were used. The *p*-value was two_tailed and $p < 0.05$ was considered to be statistically significant. Event rates (% incidence/person year) were calculated by the person year method. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using the Cox proportional hazard model, before and after the adjustments for gender, BMI, and AF type. The statistical analyses were performed using SPSS Statistics 22 (IMB Japan, Tokyo, Japan).

In this study, personal data were collected from medical charts and ethical consideration was given while protecting individual privacy. Registration began after approval of the Ethics Committee at each hospital.

Results

Patient background

Table 1 summarizes the baseline background characteristics of the study participants. Of these 453 patients were ≧80 years. The average age of the studied patients was 84.6 ± 6.4 years in men ($n = 220$) and 85.0 ± 3.8 in women ($n = 233$). Among them, 234 patients (119 men and 115 women) were aged 80–84 years, 180 (84 men, 96 women) were aged 85–89 years, 35 were aged 90–94 years (17 men, 18 women), and 4 (4 women) were 95–100 years old.

The mean body weight and body mass index (BMI) of the extreme elderly group were significantly lower than those of the control group (51.6 ± 9.9 kg vs 63.8 ± 13.0 kg, $p < 0.001$ and 22.0 ± 3.4 kg/m^2 vs 23.7 ± 4.0 kg/m^2, $p < 0.001$, respectively). Of the 453 patients in the extreme elderly group, 188 patients (41.5%) had a body weight less than 50 kg, and this proportion was significantly higher ($p < 0.001$) than the control group (13.1%). Moreover, among these patients, 159 (84.6%) also showed lower CrCl (less than 50 ml/min).

Table 1
Characteristics of patients.

	Extreme elderly	Control	*p*-value
No. of patients	453 (33.8%)	886 (66.2%)	
Age (years)	84.8 ± 5.3 (80–99)**	68.0 ± 5.3 (22–79)	<0.001
Men (%)	220 (48.6%)**	635 (71.7%)	<0.001
Women (%)	233 (51.4%)**	251 (28.3%)	<0.001
Duration of treatment (months)	11.6 ± 10.2	12.1 ± 9.1	n.s.
Paroxysmal	222 (49.0%)*	488 (55.1%)	<0.05
Persistent	231 (51.0%)	398 (44.9%)	<0.05
Body weight (kg)	51.6 ± 9.9**	63.8 ± 13.0	<0.001
<50 kg(%)	188 (41.5%)**	116 (13.1%)	<0.001
Mean (men)	55.7 ± 9.1**	66.9 ± 12.1	<0.001
Mean (women)	47.8 ± 9.1**	55.7 ± 11.6	<0.001
BMI	22.0 ± 3.4**	23.7 ± 4.0	<0.001
CrCl (ml/min)	45.4 ± 16.1**	75.1 ± 26.0	<0.001
<30	70 (15.5%)**	9 (1.0%)	<0.001
30–50	225 (49.7%)**	127 (14.3%)	<0.001
50–80	132 (29.1%)**	415 (46.8%)	<0.001
≧80	18 (4.0%)**	319 (36.0%)	<0.001
Unknown	8 (1.8%)	16 (1.8%)	n.s.
$CHADS_2$ score	2.7 ± 1.2**	1.7 ± 1.3	<0.001
CHA_2DS_2-VAS score	4.4 ± 1.4**	2.9 ± 1.6	<0.001
Heart failure	157 (34.7%)**	209 (23.6%)	<0.001
Hypertension	291 (64.2%)	566 (63.9%)	n.s.
Age ≧80 years	453 (100%)**	242 (27.3%)	<0.001
Diabetes	76 (16.8%)*	203 (22.9%)	<0.05
Stroke/TIA	129 (28.5%)**	162 (18.3%)	<0.001
Vascular disease	85 (18.8%)**	240 (27.1%)	<0.001
HAS-BLED score	2.3 ± 1.1	1.6 ± 0.8	<0.001

* $p < 0.05$.
** $p < 0.001$.
BMI: body mass index; CrCl: creatinine clearance; TIA: transient ischemic attack.

There were 222 patients (49.0%) with paroxysmal AF and 231 (51.0%) with persistent AF. Paroxysmal AF was less frequent than in the control group ($p < 0.05$). The average duration of treatment with rivaroxaban was 11.6 ± 10.2 months (0.5–36.4 months) in the extreme elderly group, and 12.1 ± 9.1 months (0.5–36.5 months) in the control group (Table 1).

$CHADS_2$ score and CHA_2DS_2-VASc score

The $CHADS_2$ score of the extreme elderly group was 2.7 ± 1.2, and the CHA_2DS_2-VASc score 4.4 ± 1.4, these scores were significantly higher than corresponding scores in the control group ($p < 0.001$). Compared to the control group, the prevalence of heart failure, stroke/transient ischemic attack (TIA) and vascular disease were significantly higher ($p < 0.001$), and the prevalence of diabetes significantly lower ($p < 0.05$) in the extreme elderly group.

HAS-BLED score

The HAS-BLED score was significantly higher in the extreme elderly group than in the control (2.3 ± 1.1 ml/min vs 1.6 ± 0.8 ml/min, respectively, $p < 0.001$).

Renal function

The average CrCl was significantly lower in the extreme elderly group than in the control group (45.4 ± 16.1 ml/min vs

Please cite this article in press as: Bando S, et al. Efficacy and safety of rivaroxaban in extreme elderly patients with atrial fibrillation: Analysis of the Shikoku Rivaroxaban Registry Trial (SRRT). J Cardiol (2017), http://dx.doi.org/10.1016/j.jjcc.2017.08.005