Safety, pharmacokinetics and pharmacodynamics of single doses of rivaroxaban – an oral, direct factor Xa inhibitor – in elderly Chinese subjects

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Summary
Rivaroxaban is a novel, oral, direct factor Xa (FXa) inhibitor for the prevention and treatment of thromboembolic disorders. The aim of this study was to investigate the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of rivaroxaban in healthy, elderly Chinese subjects. In this single-centre, single-blind, placebo-controlled, parallel-group, dose-escalation study, 79 subjects, aged 59–74 years (mean 62.8), were randomised to receive once-daily oral doses of rivaroxaban 5, 10, 20, 30 or 40 mg. Rivaroxaban was well tolerated: there was a low incidence of treatment-emergent adverse events and all events were of mild intensity. Rivaroxaban was absorbed rapidly, reaching maximum plasma concentrations within 2–4 hours. The PK of rivaroxaban were dose dependent over the dose range tested. Maximal inhibition of FXa occurred 2–3 hours after dosing and returned to baseline after 24–48 hours, reflecting rivaroxaban plasma concentrations. Inhibition of FXa was associated with dose-dependent effects on global clotting tests. There were no clinically relevant differences in rivaroxaban plasma concentrations between male and female subjects. In conclusion, rivaroxaban was well tolerated and was found to have predictable PK and PD in healthy, elderly Chinese subjects.

Keywords
Chinese subjects, factor Xa inhibitor, oral anticoagulant, rivaroxaban

Introduction
Thromboembolic disorders are a major cause of morbidity and mortality (1–4), and thromboprophylaxis with effective anticoagulants has been shown to be effective (5). Current guidelines recommend the use of anticoagulants for the prevention and treatment of venous thromboembolism (VTE), the prevention of stroke in patients with atrial fibrillation (AF) and secondary prevention in patients with acute coronary syndrome (6–8). These disorders occur more frequently in the elderly: the incidence of AF is strongly age-dependent, with a prevalence of ~10% in those aged >80 years (9). Furthermore, with an ageing population (10), the prevalence of AF in the US is projected to rise to ~12.1 million by 2050, assuming no further increase in age-adjusted incidence of AF, but 15.9 million if the increase in incidence continues (11). These factors may be problematic in an elderly population likely to require additional medication for concomitant disorders. In addition, increasing age is a risk factor for increased major bleeding with warfarin (20).

Thus, there is a clear unmet need for an effective, oral anticoagulant suitable for long-term therapy in patients of all ages (12, 21). Inhibition of factor Xa (FXa) is an attractive target for anticoagulation because FXa is an integral part of the coagulation cascade and acts at the convergence point of the extrinsic and intrinsic coagulation pathways that converge at the step of formation of the prothrombinase complex (22). FXa catalyses the conversion of prothrombin to thrombin. During the amplification phase of thrombin generation, one molecule of FXa results in the generation of more than 1,000 thrombin molecules (23). Therefore, the inhibition of FXa may block the amplification of thrombin generation (24, 25).
Rivaroxaban (26) is a novel, oral, once-daily, direct FXa inhibitor (27) approved in the EU and several other countries for the prevention of VTE after elective hip and knee replacement surgery. The efficacy and safety of rivaroxaban for the prevention and treatment of VTE were investigated in an extensive phase II programme (28–33). Following the encouraging results of these studies, rivaroxaban is currently being investigated in a worldwide phase III study programme for the prevention and treatment of thromboembolic disorders, including the prevention and treatment of VTE and the prevention of stroke in patients with AF. The finalised and reported extensive phase III RECORD programme investigated rivaroxaban in patients undergoing total hip and total knee replacement surgery. Rivaroxaban was significantly more effective than enoxaparin for the primary endpoint (the composite of any deep-vein thrombosis, non-fatal pulmonary embolism and all-cause mortality); rates of major bleeding were not significantly different (34–37).

Phase II studies of rivaroxaban were conducted predominantly in Europe and North America. To support progression into the worldwide study programme, it was important to establish the PK and PD profiles of rivaroxaban in subjects of different ethnic origins and, given the risk of thromboembolic disorders with increasing age, in elderly subjects. The present study evaluated the safety, PK and PD of rivaroxaban in healthy, elderly Chinese subjects.

Methods

Subjects

The study recruited healthy Chinese male and female subjects aged ≥60 years with a body mass index of 19–28 kg/m². Exclusion criteria included coagulation disorders (e.g. von Willebrand’s disease and haemophilia), conditions associated with an increased bleeding risk (e.g. haemorrhoids, acute gastritis, peptic ulcer) and sensitivity to nasal bleeding or concomitant use of acetylsalicylic acid, clopidogrel, non-steroidal anti-inflammatory drugs or other anti-coagulants (and their use during the two weeks preceding the study). Subjects were also excluded if they had gastrointestinal or metabolic disorders that could influence drug absorption or metabolic turnover (e.g. endocrine diseases), or were diagnosed with malignancy, endocrine diseases, or were diagnosed with metabolic disorders that could influence drug absorption or metabolic turnover (e.g. endocrine diseases), or were diagnosed with malignancy.

Study design

This was a single-centre, randomised, single-blind, placebo-controlled, parallel-group, dose-escalation study. Rivaroxaban dose steps of 5, 10, 20, 30 and 40 mg (each as a single oral dose with food) were planned. Escalation to each new dose step was dependent on the safety and tolerability of the preceding dose. The doses of rivaroxaban investigated were selected based on PK and PD data of single doses of rivaroxaban in healthy, elderly Caucasian subjects (38). For each dose step, eight male and eight female elderly Chinese subjects were enrolled: six male and six female subjects were randomised to receive rivaroxaban, and two male and two female subjects received placebo. Subjects entered the study unit the day before drug administration and fasted overnight (=9.5 hours [h]). Rivaroxaban or placebo was administered the following day within 5 minutes of completing a standardised breakfast (consisted of bread [100 g], omelette [two eggs, 110 g; salad oil, 30 g], congee [rice, 15 g] and ham sausage [90 g]). Subjects were discharged 72 h after drug administration and returned for a follow-up assessment seven days after study completion. The study was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. The study protocol and amendments were approved by the Independent Ethics Committee of the study centre and by the State Food and Drug Administration of China. All subjects participating in the study provided written, informed consent.

Safety and tolerability assessments

Subjective well-being and adverse events were assessed by questioning study participants. A physical examination was carried out and tolerability was further assessed by objective assessment of cardiovascular function (heart rate, blood pressure and electrocardiogram [ECG]), haematology, blood chemistry and urine analysis. Adverse events were classified according to their degree of severity (mild, moderate or severe) and as serious or non-serious. The incidence of treatment-emergent adverse events was classified using MedDRA (Medical Dictionary for Regulatory Activities) criteria.

Pharmacokinetic assessments

Blood samples were collected before (time 0), and 0.5, 1, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48 and 72 h after administration of rivaroxaban. Samples were collected into ammonium heparin or lithium heparin tubes; samples were then centrifuged and the plasma was decanted, frozen and stored at −20°C until analysis. Urine was collected and pooled for the time periods 0–4, 4–8, 8–12, 12–24, 24–48 and 48–72 h after rivaroxaban dosing. A sample from each time period was frozen and stored at −20°C until analysis. Frozen plasma and urine samples were analysed at a central facility (Bayer HealthCare AG, Wuppertal, Germany) by high-performance liquid chromatography coupled with a tandem mass spectrometer using an internal standard. Plasma rivaroxaban concentrations above the lower limit of quantification (0.5 μg/l) were detected with an accuracy of 99.9–107.4% and a precision of 3.5–5.6%.

Standard formulae were applied to determine primary PK parameters: area under the plasma concentration–time curve (AUC), maximum plasma concentration (C_{max}), AUC divided by dose per
kg body weight (\(\text{AUC}_{\text{norm}}\)) and \(\text{C}_{\text{max}}\) divided by dose per kg body weight (\(\text{C}_{\text{max,norm}}\)). The secondary PK parameters assessed were half-life (\(\text{t}_{\frac{1}{2}}\)), time to maximum plasma concentration (\(\text{t}_{\text{max}}\)), mean residence time (\(\text{MRT}\)), apparent volume of distribution during terminal phase (\(\text{V}_{\text{Z/f}}\)), total body clearance of drug from plasma calculated after oral administration (\(\text{CL/f}\)), amount of drug excreted in the urine (\(\text{Ae}_{\text{ur}}\)) and renal clearance (\(\text{CLR}\)).

**Pharmacodynamic assessments**

Blood samples for assessing the PD effects of rivaroxaban were collected into tubes containing sodium citrate at the same timepoints as the PK samples. The samples were centrifuged and plasma was decanted, frozen and stored at –20°C until analysis. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured in parallel at the investigator’s site and at a central facility (Bayer HealthCare AG, Wuppertal, Germany). PT was measured using Neoplastin®. FXa activity tests and the HepTest were performed only at the central laboratory (Wuppertal, Germany). The methods used for these assessments have been described in detail previously (39).

**Statistical analyses**

Demographic characteristics, laboratory variables, safety data and PD data were described by appropriate summary statistics (arithmetic mean, standard deviation [SD], median, minimum and maximum) for the original data and differences compared with baseline. For the PK data, the following were calculated for each sampling point: arithmetic mean, SD and coefficient of variation (CV), geometric mean, geometric SD and CV, minimum, median and maximum value. AUC, \(\text{C}_{\text{max}}\), \(\text{C}_{\text{max,norm}}\) and \(\text{C}_{\text{max,oral}}\) were analysed assuming log-normally distributed data, and dose proportionality and gender effects were investigated by exploratory analysis of variance (ANOVA) on the log-transformed values with the significant level of \(\alpha=0.05\). Point estimates (least-squares [LS]-means ratios) and two-sided 95% confidence intervals (CI) for these primary PK parameters were calculated by retransformation of the logarithmic data. Statistical evaluation was performed by APEX International (Taipei) using the Statistical Analysis System (SAS®) software package.

**Results**

**Subjects**

A total of 79 elderly Chinese subjects were enrolled into the study (originally, 80 volunteers entered the study; however, on the day of administering the study drug, one subject was excluded because her veins were too thin to obtain a blood sample). Three subjects were withdrawn before receiving study drug because of protocol violations; therefore, 76 subjects received study drug according to protocol and completed the study. There were no major deviations from the study protocol and data from all 76 subjects were included in the safety, PK and PD analyses. One minor deviation from the protocol was the inclusion of one subject aged 59 years and 11 months (inclusion criteria stated age \(=60\) years).

The study groups were well matched with respect to demographic characteristics (Table 1). The mean age of subjects was 62.8 years (range 59–74 years).

**Safety and tolerability**

Eight subjects reported a total of nine treatment-emergent adverse events during the study. Three of the nine events occurred after administration of placebo (one case of diarrhoea and two cases of increased alanine aminotransferase [ALT] levels). Among the subjects receiving rivaroxaban, no adverse events were reported in the 5 mg group; adverse events were reported by two subjects in the 10 mg group (three episodes of hypertension), one subject in the 20 mg group (headache) and one subject in each of the 30 mg and 40 mg groups (ECG changes). Only the latter two adverse events

<table>
<thead>
<tr>
<th>Table 1: Demographic characteristics. Values are shown as mean (range), except gender, which is shown as number (percentage).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivaroxaban dose</strong></td>
</tr>
<tr>
<td><strong>Placebo</strong>&lt;sup&gt;n=19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age, years</td>
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<tr>
<td>Gender, n (%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Weight, kg</td>
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<tr>
<td>Body mass index, kg/m²</td>
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</tbody>
</table>

<sup>a</sup>Three subjects withdrew from the study before taking the study drug: 76 subjects received study drug according to protocol and completed the study.
were considered possibly related to study medication: QT prolongation (in the 30 mg group) in a subject with a corresponding low heart rate (47 bpm) and an ST-T abnormality (in the 40 mg group) in a subject with pre-existing flat T-waves. All adverse events were of mild intensity; five events resolved without treatment and three (one ALT increase and two ECG changes) had improved by study completion.

No clinically meaningful changes in vital signs or laboratory parameters were observed after rivaroxaban administration.

### Pharmacokinetics

Rivaroxaban was absorbed rapidly, with $C_{\text{max}}$ reached within 2–4 h after administration (Fig. 1). The $t_{\text{max}}$ of rivaroxaban ranged from 4.5 (5 mg) to 9.6 (30 mg) h and was not dose-dependent (Table 2). Dose-dependent increases in $C_{\text{max}}$ were observed (Fig. 1; Table 2) and increases in AUC were almost dose proportional. Statistical analysis examining the ratios of $AUC_{\text{norm}}$ using rivaroxaban

![Figure 1: Mean rivaroxaban plasma concentration–time profiles in healthy, elderly Chinese subjects after administration of a single dose of rivaroxaban. Data shown are geometric means.](image)

### Table 2: Pharmacokinetic parameters of rivaroxaban after administration of single doses in healthy elderly Chinese subjects.

<table>
<thead>
<tr>
<th>Rivaroxaban dose</th>
<th>5 mg (n=12)</th>
<th>10 mg (n=11)</th>
<th>20 mg (n=12)</th>
<th>30 mg (n=12)</th>
<th>40 mg (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{\text{µg·h/l}}$</td>
<td>610.1 (36.6)</td>
<td>1,060 (18.0)</td>
<td>2,167 (16.7)</td>
<td>3,360 (21.8)</td>
<td>4,339 (21.6)</td>
</tr>
<tr>
<td>$AUC_{\text{male/female ratio, %}}$</td>
<td>77.9 (49.6–122.5)</td>
<td>96.5 (74.6–124.7)</td>
<td>84.5 (69.9–102.1)</td>
<td>82.5 (63.8–106.8)</td>
<td>83.8 (62.3–112.8)</td>
</tr>
<tr>
<td>$AUC_{\text{norm}, \text{µg·h/l}}$</td>
<td>7,590 (33.5)</td>
<td>6,207 (27.4)</td>
<td>6,501 (14.4)</td>
<td>6,921 (22.0)</td>
<td>6,825 (21.6)</td>
</tr>
<tr>
<td>$AUC_{\text{max}, \text{male/female ratio, %}}$</td>
<td>80.1 (52.8–121.6)</td>
<td>117.1 (80.9–169.4)</td>
<td>96.0 (79.2–116.2)</td>
<td>91.8 (68.9–122.4)</td>
<td>99.3 (71.3–138.1)</td>
</tr>
<tr>
<td>$C_{\text{max}, \text{µg/l}}$</td>
<td>121.3 (27.2)</td>
<td>228.0 (20.5)</td>
<td>386.2 (17.5)</td>
<td>550.2 (19.4)</td>
<td>670.2 (20.7)</td>
</tr>
<tr>
<td>$C_{\text{max}, \text{male/female ratio, %}}$</td>
<td>119.3 (84.7–168.1)</td>
<td>92.2 (69.3–122.7)</td>
<td>93.1 (74.1–117.0)</td>
<td>77.5 (64.3–93.3)</td>
<td>84.7 (63.6–112.9)</td>
</tr>
<tr>
<td>$C_{\text{max}, \text{norm}, \text{µg/l}}$</td>
<td>1,510 (23.7)</td>
<td>1,335 (30.1)</td>
<td>1,159 (13.6)</td>
<td>1,133 (17.5)</td>
<td>1,054 (18.1)</td>
</tr>
<tr>
<td>$C_{\text{max}, \text{norm}, \text{male/female ratio, %}}$</td>
<td>122.6 (92.2–163.1)</td>
<td>111.9 (73.8–169.7)</td>
<td>105.8 (88.4–126.5)</td>
<td>86.2 (69.9–106.3)</td>
<td>100.4 (76.0–132.6)</td>
</tr>
<tr>
<td>$t_{\text{max}, \text{h}}$</td>
<td>2 (0.5–4)</td>
<td>3 (2–4)</td>
<td>3 (1–4)</td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>$t_{\text{max}, \text{h}}$</td>
<td>4.5 (51.4)</td>
<td>9.0 (55.8)</td>
<td>8.3 (59.6)</td>
<td>9.6 (61.7)</td>
<td>8.8 (63.6)</td>
</tr>
<tr>
<td>$CL/F, \text{l/h}$</td>
<td>8.20 (36.6)</td>
<td>9.43 (18.0)</td>
<td>9.23 (16.7)</td>
<td>8.93 (21.8)</td>
<td>9.22 (21.6)</td>
</tr>
<tr>
<td>$CL/F, \text{l/h}$</td>
<td>2.70 (29.6)</td>
<td>2.78 (21.3)</td>
<td>2.56 (33.8)</td>
<td>2.87 (18.8)</td>
<td>2.45 (23.9)</td>
</tr>
<tr>
<td>$Ae_{\text{u}}, \text{%}$</td>
<td>34.4 (9.7)</td>
<td>30.1 (6.8)</td>
<td>29.4 (7.8)</td>
<td>32.2 (3.9)</td>
<td>26.9 (5.5)</td>
</tr>
<tr>
<td>$MRT, \text{hd}$</td>
<td>5.5/32.4 (3.4–8.4)</td>
<td>6.5/15.8 (5.1–8.6)</td>
<td>6.6/28.4 (4.3–13.0)</td>
<td>7.8/28.3 (4.8–12.1)</td>
<td>8.2/27.9 (5.5–15.8)</td>
</tr>
</tbody>
</table>

$^a$Point estimates (two-sided 95% confidence interval) for the ratios of the primary parameters in males and females; $^b$median (range); $^c$arithmetic means (standard deviation); $^d$geometric mean values/geometric % coefficient of variation, unless otherwise indicated. The ratios for gender for the primary pharmacokinetic parameters are shown.
10 mg as a reference, found no significant change in AUCnorm after rivaroxaban 20 mg (ratio 1.05 [95% CI 0.86–1.28]), 30 mg (1.12 [0.91–1.37]) and 40 mg (1.10 [0.89–1.36]).

AUC and Cmax tended to be higher in females than in males; however, comparison of values normalised for dose and body weight (AUCnorm and Cmax,norm) indicated that there were no clinically relevant differences in rivaroxaban PK between males and females (Table 2).

Urine excretion rates (Ae ur0–72) for the 5 mg to 40 mg dose groups ranged from 34–27% of the administered dose.

Pharmacodynamics

Rivaroxaban markedly inhibited FXa activity compared with placebo (Fig. 2). Inhibition of FXa activity reached a maximum within 2–3 h of administration and had returned to baseline 24–48 h after dosing. Maximum inhibition of FXa activity compared with baseline ranged from 32% after rivaroxaban 5 mg to 67% after rivaroxaban 30 mg (Table 3). The median rate of inhibition of FXa activity increased with increasing rivaroxaban dose from 5 mg to 30 mg; median rates of inhibition were similar for the subjects in the 10 mg and 20 mg groups, and for subjects in the 30 mg and 40 mg groups. Inhibition of FXa activity was slightly greater in females than in males (Fig. 2B).

Rivaroxaban 5–40 mg resulted in dose-dependent prolongation of PT (Fig. 3). Peak prolongation of PT occurred 1–3 h after administration of rivaroxaban, and values returned to baseline 24–36 h after dosing. Maximum median prolongation of PT compared with baseline was 2.8-fold after rivaroxaban 40 mg (Table 3). There appeared to be a slightly greater prolongation of PT in females compared with males (Fig. 3B).

Prolongation of aPTT and HepTest with rivaroxaban followed a similar pattern to inhibition of FXa activity and prolongation of PT. Prolongation of aPTT and HepTest reached a maximum of 1.8-fold and 2.8-fold increases from baseline values, respectively, after rivaroxaban 40 mg (Table 3). Maximum prolongation of aPTT and HepTest occurred 2 h after rivaroxaban administration and returned to baseline 24–48 h after administration. There was a slightly greater prolongation of aPTT and HepTest (except with rivaroxaban 5 mg in the HepTest) in females compared with males.
Discussion

In this study, rivaroxaban had predictable PK and PD in elderly Chinese subjects. Rivaroxaban was well tolerated, with a low incidence of drug-related treatment-emergent adverse events. There was no evidence for a dose-related increase in adverse events and no signs or symptoms of bleeding were reported. No serious adverse events were reported, and only two events were considered by the investigators as possibly related to rivaroxaban: mild ECG changes in two patients with either a concomitant low heart rate at baseline or a pre-existing minor ECG aberration. The effect of rivaroxaban on the QTc interval has been assessed thoroughly in a...
Rivaroxaban was absorbed rapidly in elderly Chinese subjects, reaching Cmax at 2–4 h. The PK of rivaroxaban was dose-dependent over the dose range 5–40 mg and increases in AUC tended to be dose proportional in this elderly population. Rivaroxaban produced marked inhibition of FXa activity; maximum inhibition occurred 2–3 h after dosing and returned to baseline after 24–48 h. Inhibition of FXa activity was dose-dependent for rivaroxaban 5–30 mg. The extent of inhibition of FXa activity was similar in the 10 mg and 20 mg dose groups, and in the 30 mg and 40 mg groups. Similar inhibition of FXa activity after 10 mg and 20 mg rivaroxaban in the current study may be attributable to a larger-than-expected response in the 10 mg group. The reason for this is unclear but may relate to individual variation and the small number of patients involved in the current study. The overlap at the higher doses may represent a ceiling effect – a similar effect was reported in elderly Caucasian subjects (41).

Inhibition of FXa activity was associated with prolongation of the global clotting tests PT, aPTT and HepTest, indicating effective anticoagulation. Data for PT, aPTT and HepTest followed the same profile as inhibition of FXa activity and plasma concentrations of rivaroxaban; the responses peaked at 1–3 h and returned to baseline 24–48 h after dosing.

The effect of rivaroxaban on PD parameters mirrored the plasma concentrations of rivaroxaban determined in the patients. This was consistent with previous findings that showed a close correlation between plasma concentrations and PD effects (42, 43). There were no clinically relevant gender differences in exposure to rivaroxaban after administration of single oral doses when these data were normalised for differences in body weight. Inhibition of FXa activity was slightly greater in females compared with males. Similarly, the prolongation of PT, aPTT or HepTest after rivaroxaban was slightly greater in females compared with males. However, this effect was not considered clinically relevant.

Rivaroxaban was well tolerated and demonstrated predictable PK and PD in healthy, young Chinese subjects (44). The current study showed that rivaroxaban had predictable PK and PD in elderly Chinese subjects, although exposure to rivaroxaban was moderately higher when the dosage was greater than 20 mg. The difference in rivaroxaban exposure between young and elderly Chinese subjects was smaller with the lower doses of rivaroxaban, which are those likely to be used in clinical practice (10 and 20 mg once daily [od]). Similar findings have been reported in elderly and adult Caucasian subjects (41–43). Because approximately one-third of rivaroxaban is excreted unchanged by the kidneys (45), and renal function declines with increasing age, higher plasma concentrations in elderly subjects are to be anticipated. In line with this, total body clearance of the higher doses of rivaroxaban was lower in elderly Chinese subjects compared with younger Chinese adults (44).

The phase III RECORD programme investigated the efficacy and safety of rivaroxaban for the prevention of VTE after major orthopaedic surgery. It enrolled patients from different ethnic origins with no upper age limit, and all patients received a fixed rivaroxaban dose of 10 mg od. The studies showed that rivaroxaban was significantly more effective than enoxaparin for the prevention of VTE (34–37).

Limitations of the current study included that this was a single-blinded study and investigators were aware of treatment regimens because they reviewed lab test reports for PT and aPTT according to the time schedule specified by the protocol (it made them aware of which patients received rivaroxaban). We would also like readers to be aware that none of the elderly subjects were on any concomitant medication at the time of the study (within 14 days prior to administration of test drug), which may not reflect a real-life situation.

Although there is no specific antidote antagonising the PD effect of rivaroxaban available, given that rivaroxaban has a relatively short half-life (38, 42, 43), drug discontinuation may suffice. Alongside this, appropriate symptomatic treatment, e.g. mechanical compression, surgical interventions, fluid replacement, and haemodynamic support should be considered if bleeding occurs (46).

In conclusion, the results of this study demonstrate that rivaroxaban was well tolerated among elderly Chinese subjects, and its PK and PD were predictable. These data provide valuable information for the ongoing worldwide clinical development programme for rivaroxaban, and suggest that dose adaptation depending on ethnic origin and age is not necessary with rivaroxaban.

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