Outcomes associated with non-recommended dosing of rivaroxaban: results from the XANTUS study

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Abstract

Aims: In Europe, the approved rivaroxaban dose for stroke prevention in patients with atrial fibrillation is 20 mg once daily (od), with 15 mg od recommended in patients with creatinine clearance [CrCl] 15–49 mL/min. Non-recommended doses are prescribed in real-world practice. This analysis of the XANTUS study assessed outcomes associated with non-recommended dosing and patient characteristics that may have impacted dose choice.

Methods and results: Baseline characteristics and 1-year outcomes were compared in 4464/6784 patients with known CrCl, receiving recommended or non-recommended rivaroxaban doses; 3608 (80.8%) patients received recommended doses (mean $CHADS_2$ score 1.9) and 856 (19.2%) non-recommended doses (mean $CHADS_2$ score 2.5). Incidence rate (events/100 patient-years) for the composite of treatment-emergent adjudicated major bleeding, stroke/systemic embolism and death was 7.5 (95% confidence interval [CI] 5.7–9.8) and 4.8 (95% CI 4.1–5.7) with non-recommended and recommended doses, respectively (hazard ratio 1.55; 95% CI 1.2–2.1; *P* = 0.004). Incidence rates for the components of the composite were 3.7 and 2.6, 1.4 and 0.9, and 3.5 and 1.9, respectively. Adjustment for baseline characteristics showed similar rates of the composite outcome (hazard ratio 1.06; 95% CI 0.77–1.45; *P* = 0.719). Multivariable analysis identified age, anaemia, congestive heart failure, diabetes mellitus, CrCl, lower body weight, atrial fibrillation type, and vascular disease as predictors of non-recommended dosing.

Conclusion: Non-recommended rivaroxaban dosing was associated with less favourable outcomes, possibly due to baseline characteristics, in addition to renal function, that may also affect physicians' dosing decisions.

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Introduction

The prevalence of atrial fibrillation (AF) varies from 400–475 per 100,000 population in Western Europe to 700–775 per 100,000 in North America and increases with age.[1] Thromboembolic stroke or non-central nervous system (CNS) systemic embolism (SE) is a potential complication in patients with AF, which can be reduced with appropriate anticoagulation.[2] Although vitamin K antagonists (VKAs) are effective in this setting, non-VKA oral anticoagulants (NOACs) are the guideline-preferred option.[2] NOACs have been shown to be at least as effective as warfarin in preventing stroke/non-CNS SE in patients with AF;[3-6] a meta-analysis of all phase III trials assessing the use of NOACs versus warfarin in patients with AF showed that NOACs reduced the risk of stroke/non-CNS SE, mortality, intracranial haemorrhage (ICH), and major bleeding.[7]

In the phase III ROCKET AF study, rivaroxaban was tested in a population of patients with non-valvular AF (NVAF) with moderate-to-high stroke risk (mean $CHADS_2$ score 3.5).[3] Rivaroxaban was non-inferior to warfarin for preventing stroke/non-CNS SE, and was associated with a similar incidence of major bleeding events but significantly fewer fatal bleeding and ICH events versus warfarin.[3] Based on these results, rivaroxaban was approved for stroke prevention in patients with NVAF at a dose of 20 mg once daily (od), with a 15 mg od dose recommended in patients with moderate-to-severe renal impairment (creatinine clearance [CrCl] 15–49 mL/min).[8]

In clinical trials, adherence to the protocol, including measurement of renal function and adaptation of dose, is closely monitored and all patients should receive the recommended dose of the medication being tested. This contrasts with clinical practice, where non-recommended doses may be prescribed.[9] This analysis assesses clinical outcomes in patients enrolled in XANTUS receiving recommended or non-recommended rivaroxaban

doses according to the European label,[8] and investigates potential patient characteristics that may have impacted the dose prescribed.

Methods

XANTUS was an international, prospective, observational study that investigated the use of rivaroxaban in routine clinical practice in Europe, Canada, and Israel; the study design was approved by the European Medicines Agency (EMA) and has been published previously.[10]

Study population and screening

Eligible patients aged ≥18 years with NVAF who had started rivaroxaban therapy to reduce the risk of stroke or non-CNS SE were identified. All patients provided written informed consent. Participating investigators were asked to screen all patients with AF receiving pharmacological treatment for stroke prevention, regardless of the treatment prescribed. Screening occurred before patients signed the informed consent forms; it was not permissible to collect any patient-related data from the remaining ineligible or non-consenting patients. To reduce selection bias, enrolment was consecutive and no eligible patient was to be omitted. The initial visit and initiation of rivaroxaban treatment were to take place within the enrolment period to rule out retrospective inclusion.

Medication and follow-up

Decisions about prescribing rivaroxaban were at the discretion of the treating physician; this included the dose and duration of therapy. In Europe, Israel, and Canada, the label-recommended rivaroxaban dose for stroke prevention in patients with NVAF and normal or mild renal impairment (i.e. CrCl ≥50 mL/min) is 20 mg od.[8] The rivaroxaban 15 mg od dose is the label-recommended dose for patients with moderate-to-severe renal impairment (CrCl 15–49 mL/min) in Europe/Israel and for patients with moderate renal impairment (CrCl 30–49 mL/min) in Canada. The Canadian label was updated after the completion of enrolment in XANTUS, and rivaroxaban 15 mg od can now also be used with caution in patients with

severe renal impairment (CrCl 15–<30 mL/min).[8,11] After the initial screening visit, patients were followed up at approximately 3-month intervals. Patients were followed for 1 year, or until 30 days after permanent discontinuation (if <1 year), of rivaroxaban treatment.

Study outcomes

The main outcomes reported in this analysis are adjudicated treatment-emergent major bleeding (defined using the International Society on Thrombosis and Haemostasis [ISTH] definition[12]), all-cause death, stroke/non-CNS SE, thromboembolic events (the composite of stroke, non-CNS SE, transient ischaemic attack [TIA], and myocardial infarction [MI]), and the composite endpoint of adjudicated treatment-emergent major bleeding, stroke/non-CNS SE, and all-cause death.

Study conduct

A Central Adjudication Committee (CAC) assessed major events, specifically major bleeding, symptomatic thromboembolic events, and all-cause death. The CAC had access to all patient records. Both bleeding events and thromboembolic events were documented by the investigators as adverse events (AEs). In cases of potential stroke, non-CNS SE, TIA, or MI, either from an investigator assessment or a database search, central adjudication was performed. The CAC also adjudicated the type of stroke and occurrence of a haemorrhagic transformation of ischaemic stroke. Clinical cause of death was also centrally adjudicated.

At each visit, explicit documentation was required regarding the potential occurrence of bleeding, stroke, non-CNS SE, TIA, MI, or any other AEs. Case Report Forms (CRFs) were designed to capture the data necessary for event adjudication. Additionally, the database was searched for concomitant medications, laboratory findings, or free text entries potentially indicating an undocumented AE of interest. Questionable findings from this search resulted in queries to the investigator and potentially, updates to the documentation in the CRF. Additionally, quality review and source data verification visits were performed at 61 (19.6%)

sites between Q4 2013 and Q3 2014, and documentation related to 581 patients (8.6%) was reviewed.

Study governance

The study complied with the Declaration of Helsinki, was approved by the appropriate Health Authorities, independent Ethics Committees and Independent Review Boards (as required) and was conducted in accordance with Good Pharmacoepidemiology Practice. An academic Steering Committee oversaw the design, execution, and conduct of the study, was responsible for manuscript development, had full access to all data and approved all versions of the manuscript.

Informed consent for all patients included the permission for collection and analysis of study data. In compliance with good clinical practice (GCP) standards, data management and statistical analyses were overseen by the sponsor. The lead statistician oversaw programming and validation of the statistical analyses.

Statistical analysis

Statistical analyses were descriptive and exploratory and carried out in the safety population, defined as all patients who had taken at least one dose of rivaroxaban. Only treatment-emergent events were considered, i.e. events that occurred from the day of the first rivaroxaban dose and up to 2 days after the last dose.

In this post hoc, exploratory analysis, the baseline characteristics and outcomes of patients who received rivaroxaban using a dose in accordance with the European label[8] were compared with those of patients who received a dose of rivaroxaban not in accordance with the European label (i.e. over-dosed with rivaroxaban 20 mg od when they had CrCl 15–49 mL/min, under-dosed with 15 mg od when they had CrCl ≥50 mL/min, dosed with 15 mg od when they had CrCl <15 mL/min, or received a dose that was neither 20 mg od nor 15 mg

od). Both raw incidence proportions (events/number of patients treated) and incidence rates (events/100 patient-years) are presented, with corresponding 95% confidence intervals (CIs). A Kaplan–Meier plot was generated to show the time course up to the first event of interest in each group. Crude and baseline characteristic-adjusted hazard ratios (HRs) were generated to compare outcomes between the groups. The selection of baseline characteristics for the adjustment was based on medical judgement.

A multivariable logistic regression with backwards selection procedure ($P = 0.10$) was performed to identify significant predictors of non-recommended dosing according to the European label. This *P*-value allowed for the identification of more potential predictors; a more restrictive *P*-value would have limited the number of predictors identified. In a further analysis, multivariable Cox regressions with backwards selection were carried out identifying predictors of the composite of major bleeding, stroke/non-CNS SE, and all-cause death separately for patients treated with label-recommended doses or other non-recommended doses.

Results

Patient population and dose received in relation to label recommendation

Of the 6784 patients enrolled in the XANTUS study who received ≥1 dose of rivaroxaban: 3608 (53.2%) received rivaroxaban in accordance with the European label and 856 (12.6%) received non-recommended doses; the remaining 2320 patients (34.2%) could not be classified, because of a lack of CrCl data (*Figure 1*). Of the patients who received non-recommended doses, 232 (27.1%) were over-dosed (i.e. received rivaroxaban 20 mg od instead of 15 mg od), 583 (68.1%) were under-dosed (i.e. received rivaroxaban 15 mg od instead of 20 mg od), and 41 patients (4.8%) received other non-recommended rivaroxaban doses (6 patients had CrCl <15 mL/min and received rivaroxaban 15 mg od; 6 patients received rivaroxaban doses >20 mg od; 29 patients received rivaroxaban doses <15 mg od).

Of the patients with CrCl 15–<50 mL/min, those with CrCl closer to 15 mL/min were less likely to be over-dosed than those with CrCl closer to 50 mL/min; of the patients with CrCl 15–<30 mL/min, 27% were over-dosed, and of the patients with CrCl 30–<50 mL/min, 36% were over-dosed. Most of the remaining patients in each group received the recommended dose of rivaroxaban 15 mg.

Patient demographics and clinical characteristics

The baseline demographics and clinical characteristics of patients stratified according to recommended or non-recommended dosing are shown in *Table 1*. Differences in baseline demographics between patients receiving recommended and non-recommended doses are shown in *Table S1*. The baseline characteristics of patients with unknown CrCl were very similar to those of patients receiving a recommended rivaroxaban dose. In patients receiving a non-recommended dose, the baseline characteristics of patients who were over-dosed with rivaroxaban 20 mg od were broadly similar to those of patients who were under-dosed with rivaroxaban 15 mg od; however, fewer males and more patients with prior MI were over-dosed than under-dosed. The mean $CHADS_2$ score was 1.9 in patients receiving a recommended rivaroxaban dose, 2.5 in patients who received a non-recommended dose, and 1.9 in patients with unknown CrCl at baseline. The mean HAS-BLED score was 2.0 in patients who received a recommended dose, 2.3 in patients receiving a non-recommended dose, and 1.9 in patients with unknown CrCl at baseline. Patients who received non-recommended doses were older and more likely to have concomitant congestive heart failure, prior stroke/non-CNS SE/TIA, or diabetes; they were also more frequently started on rivaroxaban while in hospital (*Table 1*).

Outcomes

The overall number of treatment-emergent adjudicated major bleeding, stroke/non-CNS SE, and all-cause death events in patients who received recommended or non-recommended rivaroxaban doses increased progressively over time (*Figure 2*). The incidence rate

(events/100 patient-years) of treatment-emergent adjudicated major bleeding, stroke/non-CNS SE, and all-cause death was 4.8 events/100 patient-years (95% CI 4.1–5.7) among patients receiving a recommended rivaroxaban dose and 7.5 events/100 patient-years (95% CI 5.7–9.8) among patients receiving a non-recommended dose (HR for non-recommended versus recommended dose = 1.55; 95% CI 1.15–2.10; *P* = 0.004) (*Table 2*). Patients who were over-dosed had 6.2 events/100 patient-years (95% CI 3.3–10.6) (HR = 1.28; 95% CI 0.73–2.25; *P* = 0.393 versus patients who received the recommended dose), whereas under-dosed patients had 7.6 events/100 patient-years (95% CI 5.4–10.4) (HR = 1.57; 95% CI 1.10–2.22; *P* = 0.012 versus patients who received the recommended dose) (*Table 3* and *Figure 3*). The incidence rate in patients whose CrCl was unknown was 2.4 events/100 patient-years (95% CI 1.8–3.2) (HR = 0.50; 95% CI 0.36–0.68; *P* <0.001 versus patients who received the recommended dose). After adjustment for baseline characteristics, differences in rates of treatment-emergent adjudicated major bleeding, stroke/non-CNS SE, and all-cause death between patients receiving recommended or non-recommended doses were no longer statistically significant (HR non-recommended versus recommended = 1.06; 95% CI 0.77–1.45; *P* = 0.719) (*Table 2* and *Figure 3*). Multivariable Cox regression analysis identified liver disease (HR = 2.55; 95% CI 1.28–5.06, *P* = 0.007) and congestive heart failure (HR = 2.14; 95% CI 1.51–3.02, *P* <0.001) as strong predictors of treatment-emergent adjudicated major bleeding, stroke/non-CNS SE, and all-cause death in patients who received recommended doses (*Table S2A*). In patients who received a non-recommended dose of rivaroxaban, congestive heart failure (HR = 1.97; 95% CI 1.16–3.36, *P* = 0.012) and hospitalisation at baseline (HR = 1.87; 95% CI 1.09–3.19, *P* = 0.022) were identified as predictors of major bleeding, stroke/non-CNS SE, and all-cause death (*Table S2B*).

The incidence rate of adjudicated treatment-emergent major bleeding events was 2.6 events/100 patient-years (95% CI 2.1–3.3) for patients who received a recommended dose, 3.7 events/100 patient-years (95% CI 2.5–5.3) for patients who received a non-recommended dose, and 0.7 events/100 patient years (95% CI 0.4–1.1) for patients whose

CrCl was unknown. Corresponding rates for stroke/non-CNS SE were 0.9 events/100 patient-years (95% CI 0.6–1.3) for patients receiving a recommended dose, 1.4 events/100 patient-years (95% CI 0.7–2.6) for patients receiving a non-recommended dose, and 0.5 events/100 patient-years (95% CI 0.3–0.9) for patients whose CrCl was unknown.

Incidence rates of all-cause death were 1.9 events/100 patient-years (95% CI 1.5–2.4) for patients receiving a recommended dose, 3.5 events/100 patient-years (95% CI 2.3–5.1) for patients receiving a non-recommended dose, and 1.4 events/100 patient-years (95% CI 0.9–2.0) for patients whose CrCl was unknown. The incidence rates of major bleeding, stroke/non-CNS SE, and all-cause death, stratified according to CrCl and label adherence are presented in *Figure 4*, but these results should be interpreted with caution because of the small sample size resulting in wide CIs.

Multivariable analysis identified the following as independent predictors of receiving a non-recommended dose of rivaroxaban: older age (odds ratio [OR] = 1.06 per 1-year increase; 95% CI 1.04–1.07); lower body weight (OR = 0.99 per 1-kg increase; 95% CI 0.99–1.00); presence of anaemia or reduced haemoglobin levels (OR = 1.78; 95% CI 1.25–2.53); CrCl ≥50 mL/min plus CrCl missing as opposed to CrCl <50 mL/min (OR = 0.54; 95% CI 0.44–0.66); presence of congestive heart failure (OR = 1.32; 95% CI 1.09–1.60), diabetes mellitus (OR = 1.33; 95% CI 1.09–1.61), or vascular disease (OR = 1.29; 95% CI 1.08–1.54); being treated by a general practitioner as opposed to a cardiologist/neurologist (OR = 0.62; 95% CI 0.46–0.83) or other specialist (OR = 0.49; 95% CI 0.31–0.78); and paroxysmal AF (OR = 0.75; 95% CI 0.60–0.93) or permanent AF (OR = 0.77; 95% CI 0.61–0.97) as opposed to first diagnosed AF (*Table 4*).

Discussion

This post hoc analysis of the XANTUS real-world study provided an opportunity to estimate the incidence rates of major bleeding, stroke/non-CNS SE, and all-cause death in patients

treated with rivaroxaban in accordance with European label recommendations versus those treated with a non-recommended dose (i.e. over-dosed with rivaroxaban 20 mg od instead of rivaroxaban 15 mg od in patients with CrCl 15–49 mL/min, or under-dosed with rivaroxaban 15 mg od instead of rivaroxaban 20 mg od in patients with CrCl ≥50 mL/min) in routine clinical practice. The incidence rate of the composite of treatment-emergent adjudicated major bleeding, stroke/non-CNS SE or all-cause death was significantly higher in patients who received a non-recommended dose versus those who received a recommended dose. This increase appeared to be driven by a higher rate of all-cause death; however, these differences were non-significant after adjustment for baseline characteristics. This suggested that where a non-recommended rivaroxaban dose was prescribed, the dosage was not selected based solely on CrCl (as recommended in the label), but was also based on other patient characteristics associated with stroke and bleeding risks such as age, lower body weight, congestive heart failure, diabetes mellitus, anaemia, or reduced haemoglobin, type of AF, and CrCl <50 mL/min as opposed to CrCl ≥50 mL/min or CrCl missing.

General practitioners were more likely to prescribe a non-recommended dose than cardiologists/neurologists or other specialists; the non-recommended doses prescribed in XANTUS may reflect more cautious prescribing in routine clinical practice in patients deemed to be frail and with a high bleeding risk, and in those with higher baseline $CHADS_2$ scores. It is well known that bleeding and stroke risk factors overlap.[2] The interpretation of the comparisons between patients receiving recommended or non-recommended doses is complicated by the inclusion of over-dosed and under-dosed patients in a single group (*Table 2*). It would be expected that the risk of thromboembolic events would increase with under-dosing (as was shown for ischaemic stroke in the edoxaban 30 mg od arm of the ENGAGE AF-TIMI 48 trial)[6] and the risk of bleeding would increase with over-dosing. However, there is no evidence that lower dosing is associated with better outcomes, and in fact it may increase thromboembolic risk, with this analysis showing that there was a trend towards a higher risk of major bleeding, stroke/non-CNS SE, and all-cause death in under-

dosed patients. It is unclear if label-recommended rivaroxaban 20 mg od would have resulted in lower incidence rates in this group; however, because these rates may be attributable to the characteristics of these patients rather than to the dose used, this question would be best addressed in randomised studies. In addition, patients who received a higher than recommended rivaroxaban dose had lower rates of major bleeding than those patients who were under-dosed, further linking outcomes in under-dosed patients to baseline characteristics rather than to the dose received. It should be noted that none of these differences between over-dosed and under-dosed patients were significant; this sub-analysis was not powered to detect differences between these groups and these trends should be interpreted with caution. The baseline characteristics identified in this study show which factors may influence dosing decisions in clinical practice, but the evidence is not sufficient to support a label recommendation for dose adjustment according to these characteristics. In the pivotal phase III ROCKET AF study, dosing was based on renal function only, and the rivaroxaban label recommends dosing accordingly.[3,8]

All-cause death was the only component of the composite outcome that was significantly different between patients receiving non-recommended versus recommended rivaroxaban doses groups, before, but not after, adjusting for baseline characteristics (*Table 2*). This suggests that patients receiving non-recommended doses could have an increased risk of death due to baseline differences in co-morbidities. Causes of death were not analysed according to dose in this study, but included cardiovascular death (41.5%), death due to bleeding (10.2%), cancer (19.5%) and infectious disease (8.5%) in the overall XANTUS population, with the remainder of patients having unexplained (7.6%) or other (13.6%) causes of death.[13]

In the ORBIT-AF II real-world registry, there were similar observations. Of 5738 patients included and treated with a NOAC, 541 (9.4%) were under-dosed, 197 (3.4%) were over-dosed, and 5000 (87%) were treated in accordance with the respective label. Patients

receiving non-recommended doses were older, more likely to be female, less likely to be treated by an electrophysiologist, and had higher CHA_2DS_2-VASc scores and ORBIT bleeding risk scores. After adjustment, over-dosing with NOACs was associated with an increased all-cause death and under-dosed patients were more likely to be hospitalised for cardiovascular endpoints.[14] In another analysis from the ORBIT-AF II registry, patients who received non-recommended, reduced-dose NOACs were at an increased risk of thromboembolic events and death. This association was no longer significant after adjustment for differences in patient characteristics.[15]

Limitations

XANTUS was a single-arm study and, as with any open-label study, the study design can introduce bias related to treatment knowledge, for example self-selection bias when patients decide whether to provide consent and selection bias due to investigators enrolling patients with intact cognitive function. The main limitation of this analysis was that it is unknown if patients with missing CrCl levels were dosed per label recommendation or not; such a lack of information is a common drawback of real-world studies. Although CrCl might not have been measured in some cases, it is also possible that some CrCl measurements were simply not documented. The baseline characteristics of these patients were very similar to those of the patients treated in accordance with the label (although a much lower proportion were hospitalised at baseline – 4.7% versus 24.1%, suggesting that these patients may have been healthier generally and probably had normal renal function). Furthermore, the incidence rates of treatment-emergent adjudicated composite and individual endpoints were much lower in these patients with missing CrCl levels than in patients receiving recommended or non-recommended dosing. In patients receiving higher than recommended versus lower than recommended doses, the number of events was too low to allow a full comparison of each outcome. Further limitations were that, due to the non-interventional design, treatment adherence and compliance were not measured and persistence was not compared between patient groups; therefore, possible differences in the duration of rivaroxaban treatment

between patient groups were not accounted for. It was not possible to ask prescribing physicians to record the reason why they selected the prescribed dose because this might have affected the choice of dose; this also made it possible to determine what proportion of patients did not have CrCl measurements in a real-world setting. The reasons for selecting the prescribed dose would have provided insight as to whether the choice of a non-recommended dose was due to prescriber error or based on the baseline characteristics of the patients. Although a large number of baseline characteristics were recorded, it is possible that other clinical characteristics that were not recorded systematically, such as chronic lung disease, concomitant therapy (e.g. steroid use), history of bleeding, recent surgery, and thrombocytopenia, could have influenced prescription decisions; these characteristics could not be adjusted for in the analysis. The lack of data on surgery also means that the higher risk of bleeding in patients with post-operative AF could not be considered when assigning patients to groups.

Conclusion

Overall, patients in the real-world XANTUS study who were treated with a non-recommended rivaroxaban dose (both over- and under-dosed) appeared to be at a higher risk of major bleeding, stroke/non-CNS SE, and all-cause death than patients receiving a recommended dose. After adjusting for the baseline characteristics of patients receiving a non-recommended dose, these differences were no longer significant. The higher event rates among patients receiving a non-recommended dose are probably related to the underlying disease rather than the dose itself. Patient characteristics, other than CrCl levels, that may affect dosing decisions were identified, which demonstrates that physicians may not always follow label recommendations. In the absence of robust evidence on the effects of patient characteristics on outcomes, however, dosing should continue to be according to the label and physician education to emphasise this should be improved.

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Conflict of interest

PA has been a consultant for Bayer, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, AstraZeneca, Sanofi, Boston Scientific, Edwards, Lundbeck, GSK, Merck, Amgen. and Kowa Pharmaceutical. S Haas has been a consultant for Aspen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, and Sanofi. S Hess and MB are employees of Bayer AG. PK has, in the past, received consulting fees and honoraria from 3M Medica, MEDA Pharma, AstraZeneca, Bayer, Biosense Webster, Boehringer Ingelheim, Daiichi Sankyo, German Cardiac Society, Medtronic, Merck, MSD, Otsuka Pharma, Pfizer/Bristol-Myers Squibb, Sanofi, Servier, Siemens, and Takeda. ML is an employee of Chrestos Concept, which received funding for this analysis from Bayer AG. AGGT has been a consultant for Bayer, Janssen Pharmaceutical Research & Development LLC, Astellas, Portola, and Takeda. AJC has been a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, and Sanofi.

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Figure legends

Figure 1 Patient disposition and rivaroxaban dosing during the XANTUS study.

Figure 2 Time to first treatment-emergent adjudicated major bleeding, stroke/non-CNS SE, or all-cause death according to recommended or non-recommended rivaroxaban dose.

Figure 3 Composite of treatment-emergent adjudicated outcomes (major bleeding, stroke/non-CNS SE, or all-cause death).

[a]Adjusted for age (continuous), sex, first available weight (continuous), hypertension, diabetes mellitus, prior stroke/TIA/non-CNS systemic embolism, congestive heart failure, hospitalised at baseline, patient treated by (general practitioner, cardiologist/neurologist, or other), anaemia, or reduced haemoglobin.

Figure 4 Incidence rates of adjudicated major bleeding, stroke/non-CNS SE, and all-cause death stratified by CrCl and recommended or non-recommended rivaroxaban dosing.

[a]Number of events and number of patients with events: 0.

[b]95% CI.

Table 1 Demographics of XANTUS patients stratified by dose received according to the European label

	Recommended dosing (*n* = 3608)	**Recommended dosing with rivaroxaban 20 mg od (n = 3211)**	**Non-recommended dosing (*n* = 856)**	**Unknown[a] (*n* = 2320)**	**Over-dosed with rivaroxaban 20 mg od (*n* = 232)**	**Under-dosed with rivaroxaban 15 mg od (*n* = 583)**
Age years, mean (SD)	70.5 (9.92)	69.3 (9.58)	76.6 (8.71)	71.2 (9.86)	76.3 (7.98)	76.7 (8.87)
<65 years, %	24	26.7	9.9	22.8	7.8	10.6
≥65 δ75 ψεαρσ, %	43.8	47	28.5	41.2	32.3	27.1
>75 years, %	32.2	26.3	61.6	36	59.9	62.3
Male, %	60.7	62.6	51.1	59.9	40.1	55.2
BMI, kg/m^2, mean (SD)	28.4 (5.0)	28.6 (5.0)	27.4 (4.8)	28.6 (5.0)	26.8 (5.4)	27.6 (4.6)
CrCl, mL/min, %						
<15	0	–	2.3	–	6	0
≥15–<30	1.5	–	2.5	–	8.6	0
≥30–<50	9.5	–	23.6	–	85.3	0
≥50–≤80	52.2	58.6	55.1	–	0	79.1

>80	36.8	41.4	14.8	0.1%[b]	0	2 0.9
Missing	0	–	1.6	99.90%	0	0
AF type, first diagnosed, %	18.5	18.3	23.1	16.8	19.8	23.5
Paroxysmal	42.9	43.6	36	38.8	33.2	37
Persistent	13.7	13.7	13	13.6	15.5	12.3
Permanent	24.8	24.1	27.6	30.4	31.5	26.8
Existing co-morbidities, %						
Hypertension	75.2	74.2	79.1	72.2	79.3	79.8
Diabetes mellitus	19.6	18.8	23.9	18.2	22.8	24.2
Prior stroke/SE/TIA	18.5	17.7	24.2	17.9	24.1	24.2
Prior MI	10	8.9	11.8	9.8	15.1	10.6
CHF	18.6	16.8	26.8	15.8	29.7	26.8
Hospitalisation at baseline, %	24.1	23.4	29.2	4.7	25.4	29.5
$CHADS_2$ score, mean (SD)	1.9 (1.3)	1.8 (1.2)	2.5 (1.2)	1.9 (1.3)	2.5 (1.3)	2.5 (1.2)
CHA_2DS_2-VASc score, mean (SD)	3.3 (1.7)	3.1 (1.6)	4.2 (1.6)	3.3 (1.7)	4.4 (1.6)	4.1 (1.5)
HAS-BLED score, mean (SD)	2.0 (1.0)	1.9 (1.0)	2.3 (1.1)	1.9 (1.0)	2.4 (1.0)	2.3 (1.1)
Concomitant antiplatelet/NSAID use, %	18.9	18.9	19.3	16.9	16.4	19.4
Prior acetylsalicylic acid therapy, %	19	18.7	16.7	17.1	11.6	19
Prior DAPT, %	1	1	1.4	0.9	0.4	1.9

AF, atrial fibrillation; BMI, body mass index; CHF, congestive heart failure; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; od, once daily; SD, standard deviation; SE, systemic embolism; TIA, transient ischaemic attack.

[a]CrCl missing.[b]2 patients erroneously had a missing dose recorded and were included in the CrCl unknown group (despite CrCl measurements being available).

Table 2 Adjudicated treatment-emergent outcomes according to recommended or non-recommended rivaroxaban dose in patients enrolled in XANTUS

	Recommended dose (*n* = 3608)		Non-recommended dose (*n* = 856)		Unadjusted HR (95% CI)	*P*-value	Adjusted HR[a] (95% CI)	*P*-value
	Incidence proportion, n (%)	Incidence rate, events/100 patient-years (95% CI)	Incidence proportion,n (%)	Incidence rate, events/100 patient-years (95% CI)	Non-recommended dose vs. recommended dose		Non-recommended dose vs. recommended dose	
Major bleeding, stroke/non-CNS SE, or all-cause death	157 (4.4)	4.8 (4.1–5.7)	57 (6.7)	7.5 (5.7–9.8)	1.55 (1.15–2.10)	0.004	1.06 (0.77–1.45)	0.719
All-cause mortality	62 (1.7)	1.9 (1.5–2.4)	27 (3.2)	3.5 (2.3–5.1)	1.86 (1.19–2.93)	0.007	1.24 (0.77–1.98)	0.378
Thromboembolic events (stroke, TIA, non-CNS SE, or MI)	62 (1.7)	1.9 (1.5–2.4)	21 (2.5)	2.8 (1.7–4.2)	1.45 (0.89–2.39)	0.138	1.19 (0.71–1.99)	0.499
Stroke/non-CNS SE	29 (0.8)	0.9 (0.6–1.3)	11 (1.3)	1.4 (0.7–2.6)	1.63 (0.81–3.27)	0.167	1.27 (0.62–2.61)	0.51
Major bleeding events	86 (2.4)	2.6 (2.1–3.3)	28 (3.3)	3.7 (2.5–5.3)	1.39 (0.91–2.13)	0.132	0.99 (0.63–1.54)	0.958
Fatal bleeding	7 (0.2)	0.2 (0.1–0.4)	3 (0.4)	0.4 (0.1–1.1)	1.84 (0.48–7.11)	0.377	2.06 (0.48–8.75)	0.328
Critical organ bleeding	26 (0.7)	0.8 (0.5–1.2)	10 (1.2)	1.3 (0.6–2.4)	1.64 (0.79–3.41)	0.182	1.37 (0.64–2.94)	0.417
ICH	15 (0.4)	0.5 (0.3–0.8)	7 (0.8)	0.9 (0.4–1.9)	2.00 (0.81–4.9)	0.131	1.76 (0.69–4.50)	0.24

[a]Adjusted for the following additional covariates: age (continuous); sex; first available weight (continuous); hypertension; diabetes mellitus; prior stroke/TIA/non-CNS SE; congestive heart failure; hospitalised at baseline; patient treated by (general practitioner, cardiologist/neurologist, other); and anaemia or reduced haemoglobin.

Table 3 Adjudicated treatment-emergent outcomes in patients enrolled in XANTUS according to non-recommended dose

	Over-dosed with rivaroxaban 20 mg od (*n* = 232)		Under-dosed with rivaroxaban 15 mg od (*n* = 583)		HR (95% CI) over-dosed vs. under-dosed	*P*-value
	Incidence proportion n (%)	Incidence rate, events/100 patient-years (95% CI)	Incidence proportion n (%)	Incidence rate, events/100 patient-years (95% CI)		
Major bleeding, stroke/non-CNS SE, or all-cause death	13 (5.6)	6.2 (3.3–10.6)	39 (6.7)	7.6 (5.4–10.4)	0.82 (0.44–1.53)	0.527
All-cause mortality	8 (3.4)	3.8 (1.6–7.5)	16 (2.7)	3.1 (1.8–5.0)	1.23 (0.53–2.88)	0.629
Thromboembolic events (stroke, TIA, non-CNS SE, or MI)	6 (2.6)	2.9 (1.1–6.3)	14 (2.4)	2.7 (1.5–4.6)	1.05 (0.4–2.74)	0.914
Stroke/non-CNS SE	2 (0.9)	1.0 (0.1–3.4)	9 (1.5)	1.7 (0.8–3.3)	0.54 (0.12–2.51)	0.435
Major bleeding events	6 (2.6)	2.9 (1.0–6.2)	20 (3.4)	3.9 (2.4–6.0)	0.74 (0.3–1.83)	0.511
Fatal bleeding	1 (0.4)	0.5 (0.0–2.6)	2 (0.3)	0.4 (0.0–1.4)	1.22 (0.11–13.46)	0.871
Critical organ bleeding	2 (0.9)	1.0 (0.1–3.4)	8 (1.4)	1.5 (0.7–3.0)	0.62 (0.13–2.9)	0.539
ICH	2 (0.9)	1.0 (0.1–3.4)	5 (0.9)	1.0 (0.3–2.2)	0.98 (0.19–5.07)	0.985

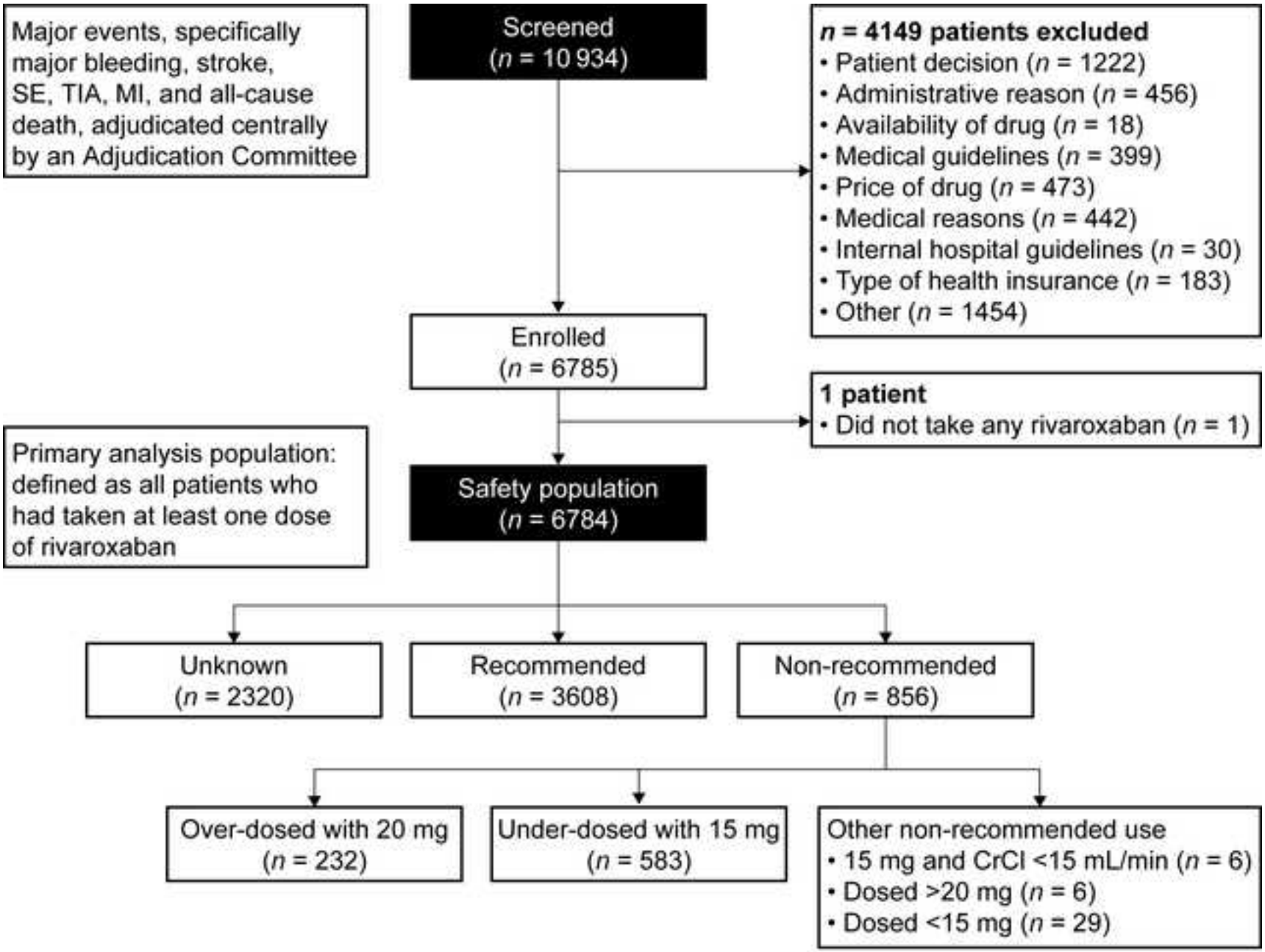
Table 4 Multivariate logistic regression analysis[a] of predictors of use of a non-recommended dose of rivaroxaban

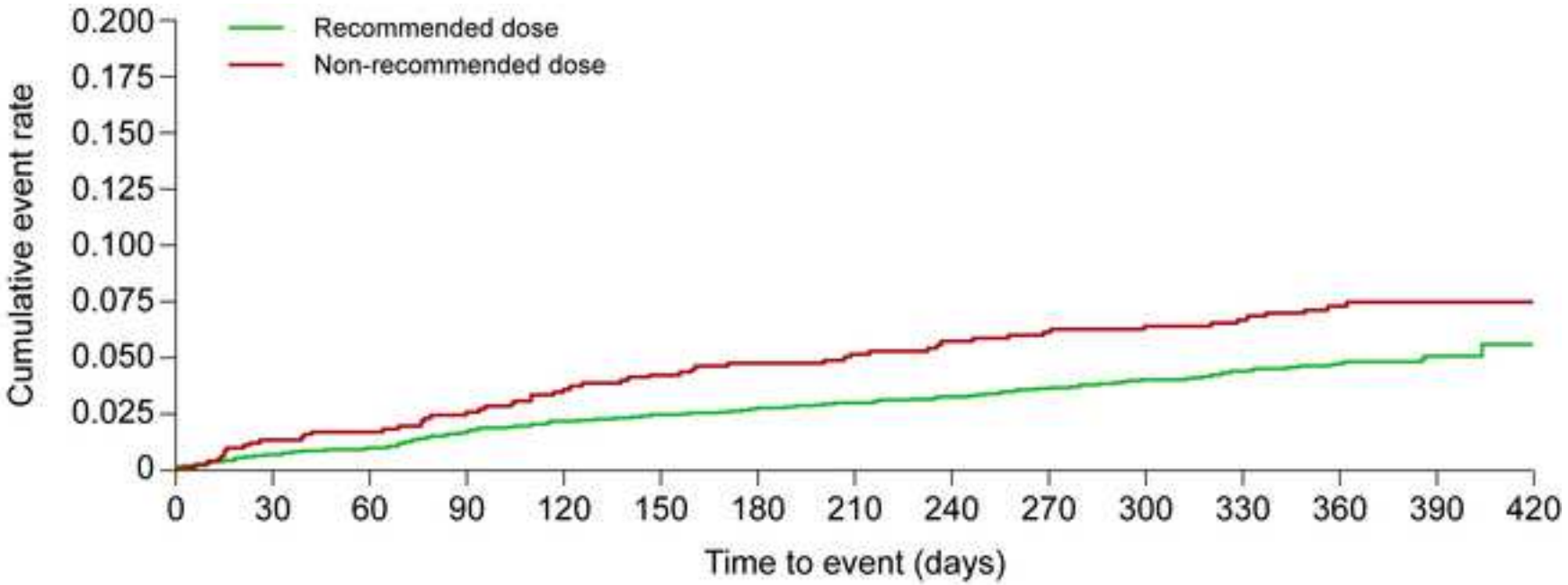
Predictor	Odds ratio (95% CI)	*P*-value
Age: per 1-year increase	1.06 (1.04–1.07)	< 0.001
First available CrCl: ≥50 mL/min or missing CrCl vs. <50 mL/min	0.54 (0.44–0.66)	< 0.001
Anaemia or reduced haemoglobin: yes vs. no	1.78 (1.25–2.53)	0.001
Patient treated by: overall		0.002
Cardiologist/neurologist vs. GP	0.62 (0.46–0.83)	0.001
Other specialist vs. GP	0.49 (0.31–0.78)	0.003
First available weight: per 1-kg increase	0.99 (0.99–1.00)	0.004
Vascular disease: yes vs. no	1.29 (1.08–1.54)	0.004
Diabetes mellitus: yes vs. no	1.33 (1.09–1.61)	0.005
Congestive heart failure: yes vs. no	1.32 (1.09–1.60)	0.005

Atrial fibrillation type: overall		0.055
Paroxysmal vs. first diagnosed	0.75 (0.60–0.93)	0.009
Persistent vs. first diagnosed	0.82 (0.62–1.09)	0.176
Permanent vs. first diagnosed	0.77 (0.61–0.97)	0.026

CI, confidence interval; CNS, central nervous system; CrCl, creatinine clearance; GP, general practitioner; SE, systemic embolism; TIA, transient ischaemic attack.

[a]A logistic regression model using a backward selection procedure was used to exclude a variable with the highest *P*-value at a time. The significance level for keeping variables in the model was *P* = 0.10. Potential predictors included in the model that were not identified as predictors of non-recommended dosing were: sex; hypertension; prior stroke/TIA/non-CNS SE; hospitalised at baseline; liver disease.

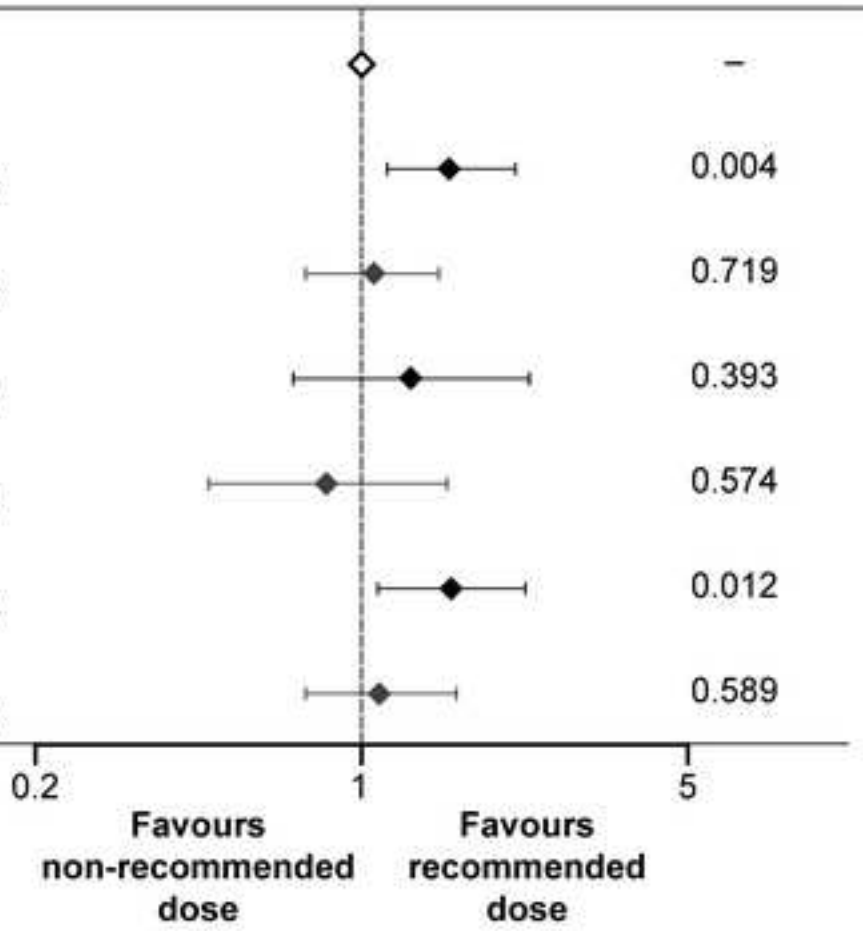




Patients at risk:

Recommended dose	3608	3468	3376	3294	3206	3153	3105	3050	3010	2967	2915	2797	2239	598	257
Non-recommended dose	856	814	794	773	750	732	718	703	691	682	674	650	542	146	57

	Patients with events, *n* (%)	Incidence rate, %/year (95% CI)	Hazard ratio (95% CI) non-recommended dose vs. recommended dose	*P*-value
Recommended dose	157 (4.4)	4.8 (4.1–5.7)	1.0	–
Non-recommended dose	57 (6.7)	7.5 (5.7–9.8)	1.55 (1.15–2.10)	0.004
			1.06 (0.77–1.45)	0.719
Over-dosed with 20 mg	13 (5.6)	6.2 (3.3–10.6)	1.28 (0.73–2.25)	0.393
			0.85 (0.48–1.51)	0.574
Under-dosed with 15 mg	39 (6.7)	7.6 (5.4–10.4)	1.57 (1.10–2.22)	0.012
			1.10 (0.77–1.58)	0.589



◆ Unadjusted HR
◆ Adjusted HR[a]