SUMMARY OF FINAL REPORT OF OBSERVATIONAL, INTERNATIONAL, MULTICENTER NON-INTERVENTIONAL STUDY GUARDIAN

Rivaroxaban real world effectiveness in patients with atrial fibrillation

Study acronym:

GUARDIAN

Study identifiers:

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1 LIST OF ABBREVIATIONS

AE	Adverse event
AF	Atrial fibrillation
AR	Adverse reaction
BMI	Body mass index
CI	Confidence interval
FAS	Full analysis set
IR	Incidence rate
PY	Patient years
SAE	Serious adverse event
SAS	Safety analysis set

2 RESULTS

The international, multicentre, non-interventional observational study Guardian, assessed the real-world effectiveness of Krka's rivaroxaban in patients with atrial fibrillation. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, in line with Good Pharmacovigilance Practice and according to local legislation for non-interventional studies in both participating countries (Bosnia and Hercegovina, Serbia). It was reviewed and approved by Independent Ethics Committees in both countries.

Data of 1118 patients from both participating countries were obtained during this study. Statistical analysis consists of data from 1092 patients due to drop out of patients with protocol deviations (missing conclusion of the study, unsigned patients, incorrect number of days between data captures).

2.1 Patient demographics

Out of 1092 patients, **42.9% (n=468) were female** and **57.1% (n=624) male patients**. Average age of patients was **67.9 years** ± 9.7 years. The oldest patient was 90 years old and the youngest 31 years old. Patients were **divided into 4 groups** according to their age. 30.5% (n=333) of patients were in the youngest age group, aged between 18 and 64 years old. 44.7% (n=488) of patients were aged between 65 and 74 years old, 16.8% (n=183) of patients were between 75 and 80 years old and remaining 8.1% of patients (n=88) were older than 81 years. Figure 1 presents distribution of patients by age groups and sex.

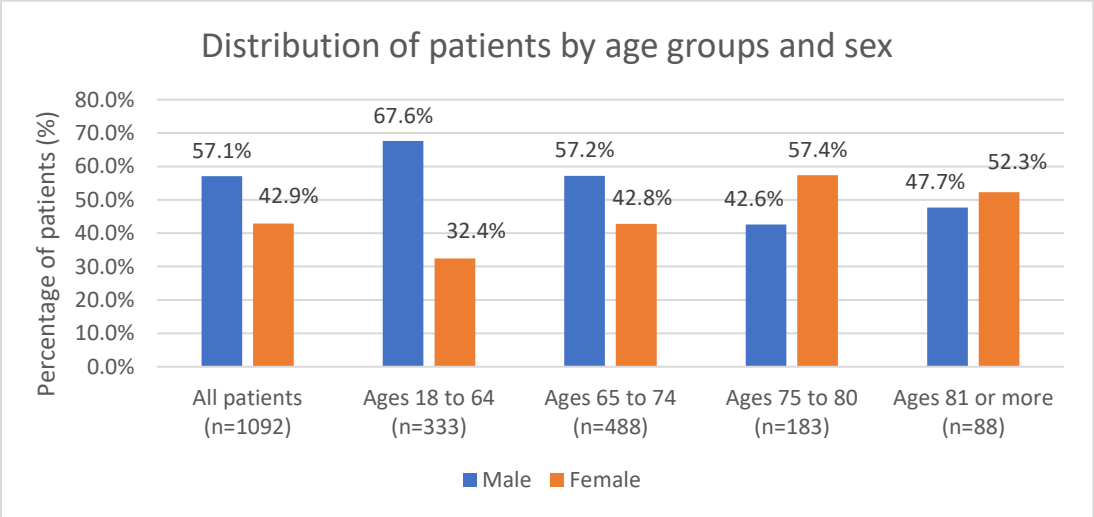


Figure 1: Distribution of patients by age groups and sex

Based on patients' BMI, more than half of patients were **overweighted** (53.8%; n=587), 255 of them were **obese** (23.4%) and little less than 23% of them had **normal wight** (22.8%; n=249). Only one patient was **underweighted** (0.1%).

At the first visit almost **60% of patients did not have smoking habits** (59.6%; n=651), **250 patients quit smoking one year or more before baseline visit** (22.9%) and **191** patents qualified as **current smoker** (17.5%). Out of all patients only **4.1%** of the patients were consuming **8 or more alcohol drinks** per week at the baseline visit (n=45).

Almost 60% (58.8%; n=642) of all patients were **diagnosed with AF prior to the baseline visit** while 41.2% (n=450) patients were **newly diagnosed**.

Out of all patients at baseline visit, 39.4% (n=430) were previously treated with anticoagulants. Among those patients, most commonly prescribed anticoagulant was **warfarin** (n=206; 47.9%), followed by **dabigatran** (n=92; 21.4%), **acenocoumarol** (n=74; 17.2%), **apixaban** (n=52; 12.1%) and **enoxaparin** (n=7; 1.6%).

At the first visit **95.1% of patients also had other comorbidities** (n=1039). In additional analysis vascular disease and thromboembolic events in the year prior to the beginning of the study were included as comorbidities. With this in mind, **95.7%** of patients had other comorbidities (n=1045). Among those patients most commonly were 2 different comorbidities per patient (34.8%; n=362), followed by 1 comorbidity per patient (28.1%; n=294) and 3 different comorbidities per patient (21.9%; n=229). 10.0% or less of patients stated that they had 4 different comorbidities (10.0%; n=105), 5 different comorbidities (4.1%; n=43) or 6 different comorbidities (0.6%; n=6). 53 patients had no comorbidities.

72.0% of the patients were multimorbid patients (n=787), meaning that they had two or more comorbidities at the time of the baseline visit. The remaining 27.9% (n=305) of the patients were non-multimorbid.

Out of patients with comorbidities, more than 90% were diagnosed with **hypertension** (n=963, 92.0%), approximately half of patients was diagnosed with **hyperlipidaemia** (n=531; 50.7%), 23.9% (n=250) patients have had diagnosis of **diabetes mellitus**, 26.8% (n=281) **heart failure,** 7.5% (n=79) **renal impairment** and 0.7% **obstructive sleep apnea** (n=7). Additionally 254 patients had vascular disease (24.3%) and 75 patients experienced symptomatic thromboembolic event in the year prior to the study (7.2%). Alongside those predefined comorbidities, 265 patients also had **other comorbidities** (25.3%). One patient could have more than one comorbidity. Figure 2 presents distribution of patients by their comorbidities.

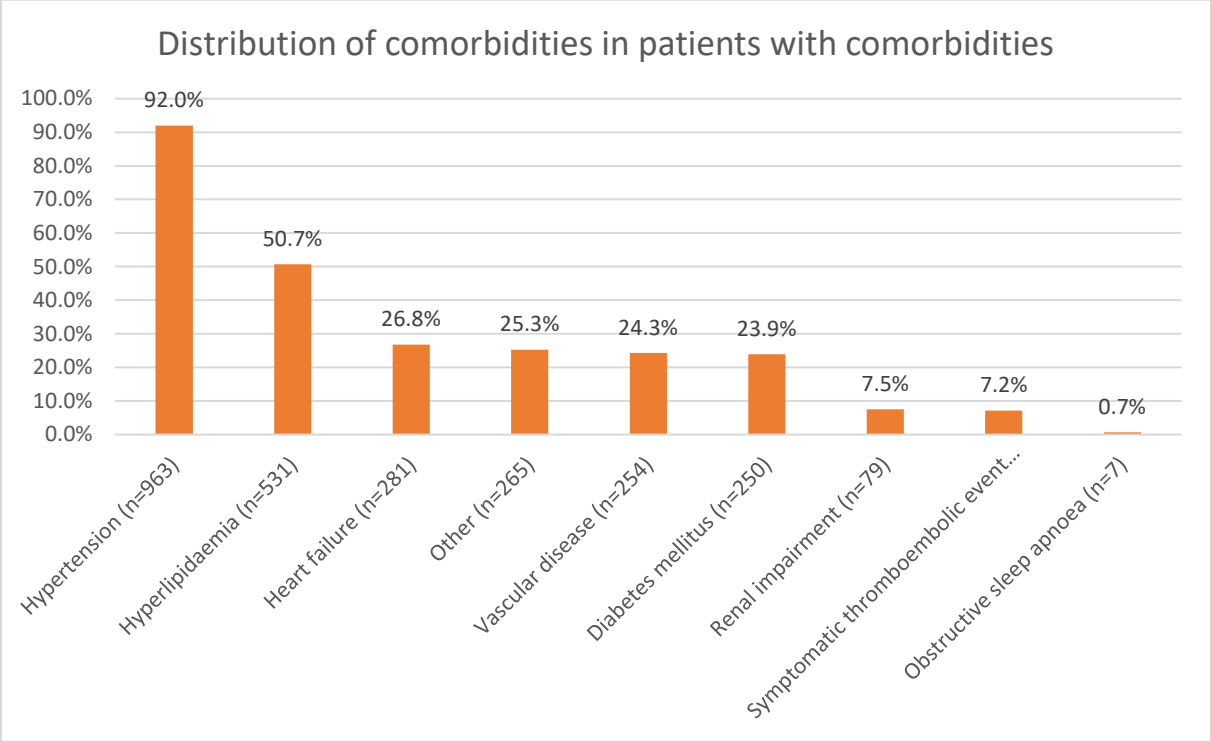


Figure 2: Distribution of patients by their comorbidities

Mean value of **CHA2DS2-VASc score** for all patients was **3.2 ± 1.6** with 0 being the lowest score and 9 the highest. 2.7% of patients (n=29) had CHA2DS2-VASc score of 0, 11.4% (n=124) had score of 1, while 21.6% (n=236) of patients had score of 2. The most patients (25.5%; n=278) had CHA2DS2-VASc score of 3, while more than 20% of patients had also score of 4 (20.6%; n=225) and almost 11% of patients (10.9%; n=119) had score of 5. Remaining high-risk groups had included less then 10% of population with 5.1% of patients (n=56) having score of 6, 1.9% (n=21) score of 7 and 0.2% (n=2) of patients had score of 8 with the same number of patients also being in the highest score group of 9.

HAS-BLED score method was used to determine the bleeding risk in patients with AF. In average all patients achieved score **1.2 ± 0.9**, with 6 being the highest score and 0 the lowest.

2.2 Primary efficacy endpoints

2.2.1 Incidence of the symptomatic thromboembolic events

After the up to 7 months observation period of 1092 patients, only **0.6% (n=7)** of them **experienced any of the symptomatic thromboembolic events**. The incidence rate (IR) of a thromboembolic event was 5.66 events per 1000 patient-years. These patients were also analyzed based on the **age subgroups**. Two of these patients were in age group between 65 and 74 years (n=488; IR=3.62), while three of them were in age group between 75 and 80 years old (n=183; IR=14.58). Each of the remaining two age groups (patients aged 18 to 64 and patients aged more than 81 years) had only one patient with thromboembolic events each. The incidence rate of the events was the lowest in

the youngest age group with 2.62 events per 1000 patient-years, while the oldest age group had the incidence rate of 10.21 thromboembolic events per 1000 patient-years. Table 1 represents the distribution of patients experiencing any symptomatic thromboembolic events by age group with incidence rates.

FAS	Patients	PY	N	IR (*)	95%-CI
All patients	1092	1237.6	7	5.66	[2.3, 11.7]
Ages 18 to 64	333	381.0	1	2.62	[0.1, 14.6]
Ages 65 to 74	488	552.9	2	3.62	[0.4, 13.1]
Ages 75 to 80	183	205.8	3	14.58	[3.0, 42.6]
Ages 81 or more	88	97.9	1	10.21	[0.3, 56.9]

Table 1: Distribution of patients experiencing any symptomatic thromboembolic events by age groups

2.3 Incidence of major bleeding events

During the entire study period **0.3% (n=3)** of the patients **experienced any of the major bleeding events** based on the investigator's assessment. After the additional medical reevaluation **2 major bleedings (0.2%)** were classified as major bleeding event The analysis of the distribution of the patients experiencing the major bleeding events was also conducted. None of those patients were aged between 75 and 80 years old, while age groups 65 to 74 and 81 or more have one of the patients with major bleeding event during the study. That represents 0.2% (n=1) of the patients in age group 65 to 74 (n=488) and 1.1% (n=1) of the patients aged 81 or above (n=88). Based on investigator's assessment there was also 1 major bleeding event in the age group from 18 to 64 (0.3%) but was additionally reclassified as clinically relevant non-major bleeding event. Table 2 represents the distribution of patients experiencing any major bleeding event by age groups.

FAS	Total	N	%	95%-CI
All patients	1092	2	0.2%	[0.0%,0.7%]
Ages 18 to 64	333	0	0.0%	[0.0%,1.1%]
Ages 65 to 74	488	1	0.2%	[0.0%,1.1%]
Ages 75 to 80	183	0	0.0%	[0.0%,2.0%]
Ages 81 or more	88	1	1.1%	[0.0%,6.2%]

Table 2: Distribution of the patients experiencing any major bleeding event by age groups

2.3.1 Safety analysis

Out of 1118 patients included in the Safety Analysis Set (SAS), 51 of them experienced adverse events (4.6%). **0.7% (n=8) of the patients experienced at least one serious adverse reaction related** to the study medicine, while 2.2% (n=25) of the patients experienced non-serious adverse reactions. 1.6% (n=18) of the patients experienced adverse events not related to the study medicine and the rest of the patients (n=1067) experienced no adverse events. Table 3 presents the distribution of the seriousness of adverse events among patients in SAS.

Patients with:	N	%
- at least one serious adverse reaction	8	0.7%
- exclusively non-serious adverse reactions	25	2.2%
- adverse events that were not related to the study medicine	18	1.6%
Patients without adverse events	1067	95.4%
	1118	100%

Table 3: Distribution of the seriousness of adverse events among patients in SAS

Among 1118 patients in Safety analysis set, 61 patients were prematurely excluded. During the observation 8 patients died, none of them were related to study medicine. 2 causes of these fatal outcomes were classified as vascular, while the remaining 6 were non-vascular.

2.4 Satisfaction

Patient's and investigator's satisfaction were measured at 2nd, 3rd and 4th data capture. Assessment of satisfaction was performed with 4 questions using Likert scale.

At data capture 4, 52.8% if patients were very satisfied with dosing regimen of Xerdoxo® (n=569) and almost 40% of patients were satisfied (n=436; 39.9%). 0.9% were neither satisfied nor dissatisfied (n=10), 1 patient was dissatisfied (0.1%) and 3 patients were very dissatisfied (0.3%). No data were

available for 73 patients (6.7%). Among patients with data, 55.8% of patients were very satisfied and 42.8% of the patients were satisfied with dosing regimen of Xerdoxo®.

Among 430 patients with previous therapy before baseline visit, 78.6% had data about the satisfaction of therapy with Xerdoxo® in comparison to the previous anticoagulant treatment on 4th data capture. Out of these patients with data, more than half assessed their response to Xerdoxo® in comparison to previous anticoagulant therapy as **very much improved** (n=174; 51.5%), approximately 40% assessed their condition as **much improved** (n=136; 40.2%), 4.7% patients reported **minimal improvement** (n=16) and 3.6% stated no change from baseline (the initiation of treatment) (n=12). No patient assessed their condition as minimally worse, much worse or very much worse since the initiation of treatment. No data were available for 92 patients.

More than half of patients (n=554; 50.7%) were very satisfied with Xerdoxo® therapy **in general** and 41.3% of patients were satisfied (n=451). 1.3% were neither satisfied nor dissatisfied (n=14) and 1 patient was dissatisfied (0.1%). No patient was very dissatisfied, and no data were available for 72 patients (6.6%). Figure 3 presents the patient's general satisfaction to Xerdoxo® therapy at 4th data capture, among patients with data, where 54.3% of patients were very satisfied in general Xerdoxo® therapy and 44.2% satisfied.

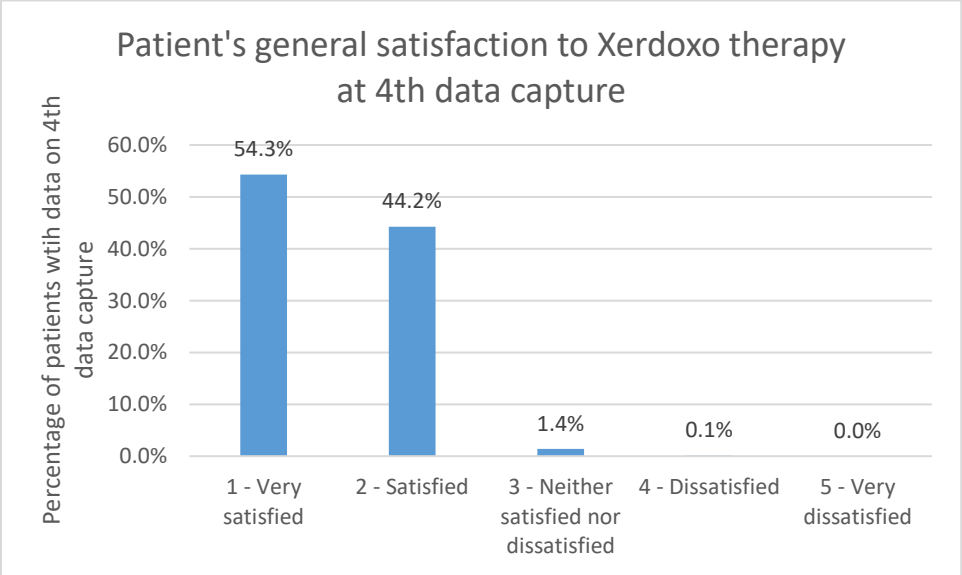


Figure 3: Patient's general satisfaction to Xerdoxo® therapy at 4th data capture

In 61.3% of cases **participating investigators** were very satisfied with Xerdoxo® treatment of their patients in general (n=669) and in 32.0% cases investigators were satisfied (n=349). In 0.5% cases investigators were neither satisfied nor dissatisfied (n=6) and in no case investigator was neither dissatisfied nor very dissatisfied. No data were available for 68 cases (6.2%). Among cases with data,

in 65.3% of cases investigators were generally very satisfied with treatment of their patients with Xerdoxo®, and in 34.1% of cases they were satisfied.

3 CONCLUSION

The GUARDIAN study provides robust real-world evidence supporting the effectiveness and safety of rivaroxaban in patients with NVAF. With a **very low rate of thromboembolic events (0.6%) and major bleeding (0.2%),** rivaroxaban demonstrated an excellent benefit-risk profile in routine clinical practice. **High patient and physician satisfaction** further underscores its role as a preferred oral anticoagulant for stroke prevention in AF.

The GUARDIAN study reinforces several key advantages of rivaroxaban in real-world practice:

- **Low incidence of thromboembolic and major bleeding events**, even in a high-risk population.
- **Predictable dosing without routine coagulation monitoring**, simplifying patient management.
- **High treatment persistence and satisfaction**, supporting adherence and long-term effectiveness.
- **Consistent safety profile**, with adverse events aligning with expectations and no new safety concerns.