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TRABAJO FIN DE MÁSTER

Efectividad y seguridad de rivaroxabán en fibrilación auricular no valvular. Datos de un registro contemporáneo español.

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Indice

Justificación de estudio

La fibrilación auricular (FA) es la arritmia cardiaca más frecuente y la principal indicación para la anticoagulación oral. Durante décadas los antivitamina K han sido la única opción en el tratamiento para la prevención del ictus en la FA. Sin embargo, estos fármacos presentan muchos inconvenientes que han llevado a la infrautilización de la anticoagulación en esta población. En los últimos años se han comercializado un nuevo tipo de anticoagulantes orales que bloquean factores claves de la coagulación y que superan muchas de las desventajas de los antivitamina K, con un perfil de riesgo/beneficio superior.

Rivaroxabán, un inhibidor del factor Xa, forma parte de este nuevo grupo de anticoagulantes orales directos. El ensayo clínico que permitió la aprobación de su uso (ROCKET-AF), demostró no ser inferior a la warfarina para la prevención de accidente cerebrovascular o embolia sistémica y evidenció una reducción marcada del riesgo de hemorragia intracraneal. Los registros internacionales publicados de fase IV han mostrado tasas más bajas de complicaciones tromboembólicas y hemorrágicas que las del ensayo pivotal. Sin embargo, en España la prescripción de estos fármacos se encuentra restringida a condiciones específicas, por lo que la efectividad y seguridad de este fármaco puede ser diferente. Por este motivo nos parece interesante determinar el perfil clínico, el manejo y las tasas de accidente cerebrovascular, hemorragia y muerte entre los pacientes bajo tratamiento con rivaroxabán en la práctica clínica, con un enfoque particular en algunos subgrupos de pacientes (ancianos, accidente cerebrovascular previo / ataque isquémico transitorio e insuficiencia renal).

A continuación se presentan los resultados de este artículo pendientes de publicación en la revista Current Medical Research and Opinion (Q1, Factor de impacto 2,665). Asímismo estos resultados han sido también presentados en el Congreso Nacional de Enfermedades Cardiovasculares celebrado en Sevilla en 2018.

Resumen

Objetivo: Conocer el perfil clínico, manejo y las tasas de complicaciones tromboembólicas y hemorrágicas en una cohorte contemporánea de pacientes con fibrilación auricular no valvular (FANV) en tratamiento con rivaroxabán, con enfoque particular en algunos subgrupos de pacientes.

Métodos: Estudio retrospectivo que incluyó a todos los pacientes con FANV que iniciaron tratamiento con rivaroxabán para la prevención del accidente cerebrovascular o la embolia sistémica entre diciembre de 2012 y diciembre de 2015. Se calcularon las tasas de los principales eventos clínicos durante el seguimiento (accidente cerebrovascular, infarto de miocardio no fatal, sangrado mayor, sangrado intracraneal y muerte).

Resultados: Se incluyeron un total de 732 pacientes (edad media 76,4 ± 92 años; 54,5% mujeres). Las comorbilidades fueron frecuentes (hipertensión arterial 87,5%; diabetes 26,5%; insuficiencia renal 24,6%; accidente cerebrovascular previo / ataque isquémico transitorio 16,8%). La media de CHA_2DS_2VASc fue 3,9 ± 1,5 y HAS-BLED 2,3 ± 0,9. El 61,9% de los pacientes que iniciaron rivaroxabán no habían recibido anticoagulación previa. Después de un período de seguimiento medio de 22,7 ± 7,4 meses, las tasas de accidente cerebrovascular, infarto de miocardio no mortal, hemorragia mayor, hemorragia intracraneal y muerte fueron 1,8, 1,0, 3,2, 0,4 y 5,5 eventos por cada 100 pacientes-año, respectivamente. Las tasas de accidente cerebrovascular y muerte fueron mayores en pacientes> 75 años (frente a ≤ 75 años) y en pacientes con accidente cerebrovascular / ataque isquémico transitorio o insuficiencia renal previa. Las tasas de hemorragia mayor fueron mayores entre los pacientes> 75 años y en pacientes con accidente cerebrovascular / ataque isquémico transitorio previo.

Conclusiones: En esta cohorte española contemporánea de pacientes con FANV tratados con rivaroxabán, los pacientes muestran elevada comorbilidad, alto riesgo tromboembólico y un riesgo de sangrado moderado. En general, las tasas de ictus y complicaciones hemorrágicas fueron bajas y similares a otros estudios previos. Estos datos sugieren que rivaroxabán es eficaz y seguro en la práctica habitual.

Palabras clave

Fibrilación auricular, rivaroxabán, anticoagulantes orales directos, ictus, hemorragia.

Abstract

Objective: To ascertain the clinical profile, management and rates of thromboembolic and bleeding complications in a contemporary cohort of patients with nonvalvular atrial fibrillation (NVAF) on rivaroxaban treatment, with a particular focus on some subgroups of patients.

Methods: Retrospective study that included all NVAF patients who started treatment with rivaroxaban for the prevention of stroke or systemic embolism between December 2012 and December 2015. Rates of outcomes (stroke, nonfatal myocardial infarction, major bleeding, intracranial bleeding and death) during follow-up were calculated.

Results: A total of 732 patients (mean age 76.4 ± 9.2 years; 54.5% women) were included. Comorbidites were common (hypertension 87.5%; diabetes 26.5%; renal insufficiency 24.6%; prior stroke/transient ischemic attack 16.8%). Mean CHA_2DS_2VASc was 3.9±1.5 and HAS-BLED 2.3±0.9. 61.9% of patients were rivaroxaban naïve users. After a mean treatment period of 22.7±7.4 months, rates of stroke, nonfatal myocardial infarction, major bleeding, intracranial bleeding, and death were 1.8, 1.0, 3.2, 0.4 and 5.5 events per 100 patient-years, respectively. Rates of stroke and death were higher in patients >75 years (vs ≤75 years) and in patients with prior stroke/transient ischemic attack or renal insufficiency. Rates of major bleeding were higher among patients >75 years and in patients with prior stroke/transient ischemic attack.

Conclusions: In this contemporary Spanish cohort of NVAF patients on rivaroxaban, patients had many comorbidities, a high thromboembolic risk and a moderate bleeding risk. Overall, rates of stroke and bleeding complications were low and similar to other previous studies. These data suggest that rivaroxaban is effective and safe in routine practice.

Keywords

Atrial fibrillation, rivaroxaban, direct oral anticoagulants, stroke, bleeding.

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Effectiveness and safety of rivaroxaban in nonvalvular atrial fibrillation: data from a contemporary Spanish registry

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Original article

Effectiveness and safety of rivaroxaban in nonvalvular atrial fibrillation: data from a contemporary Spanish registry.

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Abstract

Objective: To ascertain the clinical profile, management and rates of thromboembolic and bleeding complications in a contemporary cohort of patients with nonvalvular atrial fibrillation (NVAF) on rivaroxaban treatment, with a particular focus on some subgroups of patients.

Methods: Retrospective study that included all NVAF patients who started treatment with rivaroxaban for the prevention of stroke or systemic embolism between December 2012 and December 2015. Rates of outcomes (stroke, nonfatal myocardial infarction, major bleeding, intracranial bleeding and death) during follow-up were calculated.

Results: A total of 732 patients (mean age 76.4±9.2 years; 54.5% women) were included. Comorbidites were common (hypertension 87.5%; diabetes 26.5%; renal insufficiency 24.6%; prior stroke/transient ischemic attack 16.8%). Mean CHA_2DS_2-VASc was 3.9±1.5 and HAS-BLED 2.3±0.9. 61,9% of patients were rivaroxaban naïve users. After a mean treatment period of 22.7±7.4 months, rates of stroke, nonfatal myocardial infarction, major bleeding, intracranial bleeding, and death were 1.8, 1.0, 3.2, 0.4 and 5.5 events per 100 patient-years, respectively. Rates of stroke and death were higher in patients >75 years (vs ≤75 years) and in patients with prior stroke/transient ischemic attack or renal insufficiency. Rates of major bleeding were higher among patients >75 years and in patients with prior stroke/transient ischemic attack.

Conclusions: In this contemporary Spanish cohort of NVAF patients on rivaroxaban, patients had many comorbidities, a high thromboembolic risk and a moderate bleeding risk. Overall, rates of stroke and bleeding complications were low and similar to other previous studies. These data suggest that rivaroxaban is effective and safe in routine practice.

Keywords: atrial fibrillation; bleeding; rivaroxaban; stroke.

Introduction.

Anticoagulation is recommended for the prevention of thromboembolic complications in most patients with nonvalvular atrial fibrillation (NVAF)[1]. Despite vitamin K antagonists (VKA) effectively reduce the risk of stroke in AF patients, they have many limitations, such as frequent interactions with food and drugs, periodic determinations of anticoagulation activity, multiple dosage adjustments, etc. that have led to an underuse of oral anticoagulation in AF population in clinical practice[2-4]. Direct oral anticoagulants (DOACs) do not have these disadvantages, and they have a better benefit/risk profile than VKA[5,6]. In fact, the introduction of DOACs in routine practice has increased the overall anticoagulation rates in patients with NVAF[7-9].

The ROCKET-AF trial demonstrated in patients with a very high thromboembolic risk that rivaroxaban was noninferior (intention-to-treat population) or even superior (safety, as-treated population) to warfarin for the prevention of stroke or systemic embolism and exhibited a marked reduction in the risk of intracranial, fatal and critical bleedings[10]. International registries have reported lower rates of thromboembolic and bleeding complications than those of the ROCKET-AF trial, mainly due to a more favorable clinical profile[11-15]. However, the great majority of these registries have analyzed rates of stroke and bleeding in the overall AF population, but not in AF patients according to some particular conditions.

On the other hand, since reimbursement is restricted to some specific conditions in Spain, the prescription of DOACs in this country has been lower than in other Western countries[16], and, consequently, the experience with these drugs is more limited[17]. Although some studies about the use of DOACs in clinical practice in Spain have been published in the last years[18-22], the information currently available remains very scarce and more studies are warranted.

The objective of this study was to ascertain the clinical profile, management and rates of stroke, bleeding and death of patients taking rivaroxaban in clinical practice, with a particular focus on some subgroups of patients (elderly, prior stroke/ transient ischemic attack [TIA], and renal insufficiency).

Methods.

The study was conducted according to the Declaration of Helsinki and the protocol was reviewed and approved by the local Clinical Research Ethics Committee. A preliminary analysis of this study has been previously published[23].

Study population and design.

In this study with a retrospective design, all NVAF patients who started treatment with rivaroxaban for the prevention of stroke or systemic embolism, between December 2012 and December 2015, in two health areas belonging to two tertiary hospitals were included.

The clinical characteristics of patients as well as data from antithrombotic treatment and outcomes were recorded in detail by cardiologists and hematologists trained for this purpose. Data were collected from the clinical history of patients. With regard to the clinical characteristics of patients, the following variables were recorded: biodemographic data (age, sex, body mass index), type of AF (paroxysmal/persistent AF, permanent AF), thromboembolic and bleeding risk (CHA_2DS_2-VASc and HAS-BLED scores), cardiovascular risk factors (hypertension, diabetes, smoking), vascular disease (renal insufficiency, prior stroke/TIA, heart failure, ischemic heart disease, peripheral artery disease, systemic embolism), factors that increase the risk of bleeding (concomitant use of antiplatelets, prior major bleeding, excessive alcohol consumption), and other conditions such as chronic obstructive pulmonary disease and cancer. In addition, hemoglobin levels and the creatinine clearance (CrCl) calculated according to the Cockroft-Gault method were also recorded[24]. With regard to the antithrombotic therapy, the prior use of anticoagulant treatment, and the dose of rivaroxaban prescribed were recorded. The dosage of rivaroxaban was prescribed according to physicians´ judgment.

Follow-up and clinical outcomes.

Patients were followed-up from the date they started treatment with rivaroxaban. The follow-up was performed by cardiologists and hematologists specifically trained for this study. Clinical events were recorded in 99.7% of patients. All events recorded during the study were validated by an expert committee of 3 investigators of the study.

The study outcomes were stroke, nonfatal myocardial infarction, major bleeding, intracranial bleeding and death. Stroke was defined as any clinical manifestation of acute cerebral ischemia or hemorrhage that was ascertained by objective diagnostic/imaging testing. Hemorrhagic transformation of ischemic stroke was not considered to be hemorrhagic stroke[25]. Myocardial infarction was defined as the detection of rise in cardiac biomarkers of necrosis with at least one measurement above the 99th percentile upper reference limit, together with evidence of myocardial ischemia with at least one of the following: electrocardiographic changes indicative of new ischemia (new ST-T changes or new left bundle branch block), new pathological Q waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality[26]. Major bleeding was defined according to 2005 ISTH (International Society on Thrombosis and Haemostasis bleeding scale) criteria[27]. Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage. Deaths were classified as cardiovascular, non-cardiovascular and undetermined. CV deaths included deaths that resulted from an acute myocardial infarction, sudden cardiac death, and death due to heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, and other cardiovascular causes[28].

The clinical profile of patients, as well as the thromboembolic and bleeding events were analyzed according to different conditions (age ≤75 vs >75 years; no prior stroke/TIA vs prior stroke/TIA; CrCl <50 vs ≥50 ml/min/1.73m^2).

Statistical analysis

Mean and standard deviation and percentages were used to describe the quantitative and qualitative variables, respectively. Categorical variables were compared with the Chi-square test or the Fisher exact test, according to the sample size. When two means were compared, the t-student test or the U-Mann-Whitney test were used as appropriate. Outcomes during treatment with rivaroxaban were calculated as events per 100 patient-years. Survival curves were calculated using the Kaplan-Meier method and Cox regression analysis. Statistical significance was set at a p value of less than 0.05. The statistical analysis was performed using SPSS 21.0 (SPSS Inc., Chicago, IL).

Results.

Between December 2012 and December 2015, a total of 732 patients started treatment with rivaroxaban. Overall, mean age was 76.4±9.2 years, 54.5% women, and 46.6% had permanent AF. The presence of cardiovascular risk factors and vascular disease was common (87.5% had hypertension, 26.5% diabetes, 24.6% CrCl <50 ml/min/1.73m^2 and 16.8% prior stroke/TIA). Mean CHA_2DS_2-VASc was 3.9±1.5 (CHA_2DS_2-VASc ≥2 95.5%) and mean HAS-BLED 2.3±0.9 (HAS-BLED ≥3 38.3%). Most patients were anticoagulation-naïve users (61.9%), followed by those who switched from VKA (36.6%) and those from other DOAC (1.5%). With regard to the dosage of rivaroxaban, 52.3% of patients were taking rivaroxaban 20 mg and the remaining 47.7% rivaroxaban 15 mg (table 1).

During the follow-up period (22.7±7.4 months), the rates of stroke, major bleeding, intracranial bleeding and cardiovascular death were 1.8, 3.2, 0.4, and 2.0 events per 100 patient-years, respectively (Table 2). Among patients with major bleeding, 47.7% were gastrointestinal, 13.6% hematoma, 11.4% intracranial, 4.5% otorhinolaryngology, 4.5% genitourinary, 2.3% retroperitoneal, 2.3% pericardial, 2.3% intramuscular, 2.3% pulmonary and 9.1% others. Although some bleedings occurred at the beginning of the treatment, most episodes occurred during the follow-up. The concomitant use of anti-platelet therapy did not significantly increase the risk of major bleeding. Among patients with major bleeding, 47.7% were gastrointestinal, 13.6% hematoma, and 11.4% intracranial (Table 2). The proportion of patients with stroke and major bleeding was higher as CHA_2DS_2-VASc and HAS-BLED scores increased, respectively (figures 1 and 2).

The clinical characteristics and outcomes were analyzed according to age, renal insufficiency or prior stroke/TIA. With regard to age, compared with younger patients, those subjects aged 75 years or older were more commonly women, had more renal insufficiency, prior stroke/TIA, heart failure, prior major bleeding, cancer and a higher thromboembolic and bleeding risk, but had a lower body mass index, less excessive alcohol consumption and were less active smokers (table 3).

Compared with patients without stroke/TIA, those patients with prior stroke/TIA were older, had a higher thromboembolic and bleeding risk, more renal insufficiency, but less diabetes. Compared with patients with CrCl ≥50 ml/min/1.73m^2, those patients with CrCl <50 ml/min/1.73m^2 were older, more frequently female, had a higher thromboembolic and bleeding risk, and more vascular disease (prior stroke/TIA, heart failure, ischemic heart disease and peripheral artery disease) (table 3). The dosage of 15 mg of rivaroxaban was properly prescribed in 74.8% of patients with CrCl<50 ml/min/1.73m^2 whereas the dosage of 20 mg of rivaroxaban was properly prescribed in 60.4% of patients with CrCl ≥50 ml/min/1.73m^2 (table 3).

Compared with younger patients, patients >75 years had higher rates of stroke, death and major bleeding, with a similar risk of nonfatal myocardial infarction and intracranial bleeding. This similarly occurred among patients with prior stroke/TIA compared with patients without prior stroke/TIA (higher rates of stroke, death and major bleeding). Patients with renal insufficiency had higher risk of stroke and death, but not major bleeding, compared with patients without renal insufficiency. Despite no significant differences were found between groups regarding the risk of

intracranial bleeding, there was a trend towards more events in elderly patients. These data were confirmed in the Kaplan-Meier analyses (table 4, figure 3).

Discussion.

In this study, a wide sample of patients with NVAF newly treated with rivaroxaban in routine practice was analyzed. In this contemporary real-life study, patients were old, had many comorbidities, a high thromboembolic risk and approximately 38% of patients had a high bleeding risk. Despite that, after nearly 2 years of treatment, rates of stroke, bleeding and cardiovascular death were low.

Compared with patients included in the rivaroxaban arm of the ROCKET-AF trial, our patients were older (76.4 vs 73 years). In both studies, thromboembolic risk was high (CHA_2DS_2-VASc 3.9 and $CHADS_2$ 3.5, respectively)[10]. XANTUS was an international, multicenter, non-interventional and prospective study of patients newly started on rivaroxaban. Compared with the XANTUS study, our patients were older and had a higher thromboembolic risk (76.4 vs 71.5 years, CHA_2DS_2-VASc 3.9 vs 3.4)[11]. In Dresden NOAC registry, median age was 74 years[12]. Therefore, our patients were older and consequently, our data may provide relevant information about a population with NVAF that has not been clearly characterized in clinical practice. Overall, rates of stroke, major bleeding, and intracranial bleeding were 1.8, 3.2, and 0.4 events per 100 patient-years, respectively. In the rivaroxaban arm of the ROCKET-AF trial, these figures were 1.7, 3.6, and 0.5, respectively[10], and in the XANTUS study 0.7, 2.1 and 0.4, respectively[11]. In the Dresden NOAC Registry, in the on-treatment analysis, rates of stroke/TIA/systemic embolism and major bleeding were 1.7 and 3.0 per 100 patient-years, respectively[29]. Therefore, in our study, rates of stroke and bleeding were closer to those reported in the ROCKET-AF trial than in the XANTUS study, but similar to those of the Dresden NOAC Registry. This may be related with the different clinical profile of patients included in these studies, as well as disparities in clinical practices and medical authority politics. In summary, overall, in our study, rates of thromboembolic and bleeding outcomes were in line with those reported in other registries and in the ROCKET-AF trial, suggesting that rivaroxaban is effective and safe in the whole spectrum of AF population in clinical practice.

In our study, compared with younger patients, elderly patients had more comorbidities and a higher thromboembolic risk, but also an increased risk of bleeding. Of note, rates of stroke, and major bleeding were greater among elderly patients. In the NONAVASC registry that included elderly patients with NVAF hospitalized in Internal Medicine departments, despite these patients had many comorbidities and a high thromboembolic risk, less than 60% of patients were anticoagulated[30]. The risk of stroke markedly increases with age and unless contraindicated, anticoagulation is clearly recommended in elderly patients[1]. In fact, antiplatelets are not effective for reducing the risk of stroke in this population but increase the bleeding risk[31]. On the other hand, despite dependency, frailty, cognitive impairment and polymedication are common in elderly patients with AF, the majority of anticoagulated elderly patients in Spain are taking VKA, despite the limitations of these drugs when compared with DOACs[32]. In ROCKET-AF, despite elderly patients had higher rates of stroke and major bleeding, the relative efficacy and safety of rivaroxaban was independent of age[33]. Our data showed that despite rates of outcomes were higher in elderly population, anticoagulation with rivaroxaban could be a good alternative in this population.

Renal insufficiency increases both the risk of stroke and bleeding[34]. In our study, those patients with renal insufficiency were older, had more comorbidities and a higher thromboembolic and bleeding risk. In addition, rates of stroke were higher among patients with renal insufficiency. Therefore, in AF patients with chronic kidney disease is mandatory to assure an adequate anticoagulation, in order to achieve the best benefit risk profile. This is more important in the case of DOACs, considering that the dosage of all of them depends on renal function[10]. In the ROCKET-AF trial, patients with AF and moderate renal insufficiency had higher rates of stroke and bleeding, but

the relative efficacy and safety of rivaroxaban was independent of renal function[35]. Similarly, our study showed that rates of stroke were higher in this population in routine practice, but with an acceptable efficacy/safety profile.

Patients with AF and prior stroke/TIA are at very high risk of developing new thromboembolic events and anticoagulation is mandatory in this population[36]. In our study, rates of stroke, and major bleeding were greater among patients with prior stroke/TIA. In the ROCKET-AF trial, the relative efficacy and safety of rivaroxaban compared with warfarin was independent of the history of previous stroke or TIA[37]. In addition, it has been reported that the early treatment with rivaroxaban is well tolerated, effective and safe for the secondary prevention of patient with AF in routine practice[38]. Our study showed that despite patients with prior stroke/TIA were old and had a high thromboembolic and bleeding risk, rivaroxaban was effective and safe in this population.

In our study, 62% of patients were rivaroxaban naïve users and only 37% switched from VKA. These numbers are in line with the prescription patterns reported by the countries in our neighborhood[39]. However, our results differed from those reported in some Autonomous Communities in Spain, due to disparities in the prescription criteria between Autonomous Communities because of lack of reimbursement for some clinical conditions[40].

With regard to the dosage of rivaroxaban, approximately 52% of patients were taking rivaroxaban 20 mg and the remaining 48% rivaroxaban 15 mg. In the XANTUS study, these numbers were approximately 79% and 21%, respectively[11]. Our data suggest that in a significant proportion of patients, rivaroxaban was not prescribed properly, mainly due to the use of lower doses than indicated in some subjects, particularly in elderly patients. In the last years, a number of studies have shown that prescribing the unsuitable dose of DOACs is common in clinical practice, particularly with low doses[21,41]. This is important, because the incorrect prescription of DOACs could reduce the efficacy and safety of DOACs[17]. Therefore, more efforts are required to prescribe DOACs more properly.

Since this was a retrospective study, no control group was available, and the relative effectiveness and safety of rivaroxaban compared with other antithrombotic treatments could not be determined. However, this type of design is the best to exhibit a picture of the current management of patients in routine practice, since physicians` attitude is not influenced by participating in a study. In addition, less than 5% of data were missing, emphasizing the robustness of the results. Despite the overall analysis was not adjusted for any comorbidities, specific analyses according to age, prior stroke/TIA and renal function were performed. On the other hand, all patients came from the south-east Spain. Consequently, this increases the homogeneity of management and the internal validity but decreases the external validity of the results. The results of our study can only be extended to patients with a comparable clinical profile and attended in a similar heath care system.

Conclusions.

In this wide cohort of elderly subjects with NVAF and a high thromboembolic risk who started treatment with rivaroxaban for the prevention of stroke, after nearly 2 years of treatment, rates of stroke, major bleeding, and intracranial bleeding were 1.8, 3.2, and 0.4 events per 100 patient-years, respectively. These numbers were in accordance with previous studies, emphasizing that rivaroxaban is effective and safe in the whole spectrum of AF population in clinical practice. The dosages of 15 mg and 20 mg of rivaroxaban were properly prescribed in approximately 75% and 60% of patients, respectively. As a result, more efforts are needed to reduce gaps in the prescription of rivaroxaban in routine practice.

Transparency

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Table and figure legends

Figure 1. Proportion of patients with stroke according to CHA_2DS_2-VASc score.

Figure 2. Proportion of patients with major bleeding according to HAS-BLED score.

Figure 3. Kaplan-Meier curves of death, stroke and major bleeding, Thromboembolic and bleeding events according to age, prior stroke/TIA and renal function.

Table 1. Clinical characteristics of the study population (n=732).

Table 2. Thromboembolic and bleeding events in the overall study population (n=732).

Table 3. Clinical characteristics of the study population according to age, prior stroke/TIA and renal function.

Table 4. Thromboembolic and bleeding events according to age, prior stroke/TIA and renal function.

Table 1. Clinical characteristics of the study population (n=732).

Variable	Value
Biodemographic data	
Age (years)	76.4±9.2
Age >75 years (%)	60.5
Sex, female (%)	54.5
Body mass index (Kg/m^2)	30.9±5.5
Type of AF (%)	
Paroxysmal/persistent	53.4
Permanent	46.6
Thromboembolic and bleeding risk	
CHA_2DS_2-VASc	3.9±1.5
CHA_2DS_2-VASc ≥2 (%)	95.5
HAS-BLED	2.3±0.9
HAS-BLED ≥3 (%)	38.3
Cardiovascular risk factors	
Hypertension (%)	87.5
Diabetes (%)	26.5
Smoking (%)	
Never	79.2
Current	6.3
Former (>1 year)	14.5
Vascular disease	
CrCl<50 ml/min/1.73m^2 (%)	24.6
Prior stroke/TIA (%)	16.8
Heart failure (%)	14.7
Ischemic heart disease (%)	11.3
Peripheral artery disease (%)	3.2
Systemic embolism (%)	0.6
Factors that increase the risk of bleeding	
Antiplatelets (%)	8.8
Prior major bleeding (%)	5.6
Excessive alcohol consumption (%)	1.7
Other conditions	
Chronic obstructive pulmonary disease (%)	16.5
Cancer (%)	9.0
Biochemical data	
Hemoglobin (g/dL)	13.5±1.7
CrCl (Cockroft-Gault, ml/min/1.73m^2)	69.4±28.2
Anticoagulant treatment	
Prior use of VKA (%)	36.6
Prior use of other DOACs (%)	1.5
Dosage of rivaroxaban (%)	
15 mg	47.7
20 mg	52.3

AF: atrial fibrillation; CrCl: creatinine clearance; VKA: vitamin K antagonists: DOACs: direct oral anticoagulants; TIA: transient ischemic attack.

Table 2. Thromboembolic and bleeding events in the overall study population (n=732).

Variable	Value
Death, % (events per 100 patient-years)	10.4 (5.5)
No cardiovascular	6.6 (3.5)
Cardiovascular	3.8 (2.0)
Stroke	0.4 (0.05)
Stroke, % (events per 100 patient-years)	3.4 (1.8)
Nonfatal myocardial infarction, % (events per 100 patient-years)	2.0 (1.0)
Intracranial bleeding, % (events per 100 patient-years)	0.7 (0.4)
Major bleeding, % (events per 100 patient-years)	6.0 (3.2)
Fatal major bleeding, % (events per 100 patient-years)	0.7 (0.4)

Table 3. Clinical characteristics of the study population according to age, prior stroke/TIA and renal function.

Variable	Age ≤75 years (n=289; 39.5%)	Age >75 years (n=443; 60.5%)	P	No prior stroke /TIA (n=605; 83.2%)	Prior stroke /TIA (N= 122; 16.8%)	P	CrCl<50 ml/min/1.73m^2 (N= 180; 24.6%)	CrCl ≥50 ml/min/1.73m^2 (N=552; 75.4%)	P
Biodemographic data									
Age (years) Age >75 years (%)	67.3±6.9 0	82.4±4.3 100	<0.001 <0.001	75.8±9.3 57.8	79.6±7.9 74.6	<0.001 <0.001	82.5±5.788.1	74.0±9.350.0	<0.001 <0.001
Sex, female (%)	45.0	60.7	<0.001	54.0	58.2	NS	66.4	50.2	0.001
Body mass index (Kg/m^2)	32.3±6.1	30.1±4.9	0.021	31.1±5.5	30.4±5.6	NS	28.8±4.7	31.7±5.6	<0.001
Type of AF (%) Paroxysmal/persistent Permanent	 57.0 43.0	 50.9 49.1	 0.01	 53.7 46.3	 51.7 48.3	 NS	 53.2 46.8	 53.3 46.7	 NS
Thromboembolic and bleeding risk									
CHA_2DS_2-VASc	2.9±1.3	4.5±1.3	<0.001	3.5±1.3	5.8±1.1	<0.001	4.8±1.3	3.6±1.4	<0.001
HAS-BLED	2.0±0.9	2.5±0.8	0.001	2.1±0.8	3.3±0.8	<0.001	2.7±0.8	2.2±0.9	<0.001
Cardiovascular risk factors									
Hypertension (%)	85.4	88.8	NS	87.8	86.1	NS	92.3	88.8	NS
Diabetes (%)	27.4	26.0	NS	27.9	19.7	0.036	31.5	27.2	NS
Smoking (%) Never Current Former (>1 year)	 68.8 10.8 20.4	 86.1 3.4 10.5	 <0.001	 79.2 6.3 14.5	 79.5 6.6 13.9	 NS	 86.7 3.5 9.8	 75.6 7.1 17.3	 0.019
Vascular disease									
CrCl<50 ml/min/1.73m^2 (%)	7.2	36.5	<0.001	22.7	33.7	0.023	100	0	<0.001
Prior stroke/TIA (%)	10.8	20.7	<0.001	0	100	<0.001	23.8	15.3	0.023
Heart failure (%)	11.1	17.1	0.032	13.7	19.7	NS	28.7	10.3	<0.001
Ischemic heart disease (%)	10.4	11.9	NS	10.9	13.1	NS	16.8	10.5	0.035
Peripheral artery disease	4.2	2.5	NS	2.6	5.7	NS	6.3	1.8	0.018

(%)									
Systemic embolism (%)	0.7	0.5	NS	0.5	0.8	NS	0	0.7	NS
Factors that increase the risk of bleeding									
Antiplatelets (%)	8.7	8.9	NS	7.9	13.1	NS	12.2	8.3	NS
Prior major bleeding (%)	2.4	7.7	0.003	4.3	12.3	0.002	11.2	3.2	0.001
Excessive alcohol consumption (%)	3.5	0.5	0.002	1.8	0.8	NS	0	2.5	0.043
Other conditions									
Chronic obstructive pulmonary disease (%)	14.9	17.5	NS	16.2	18.0	NS	16.8	16.7	NS
Cancer (%)	7.9	13.9	0.03	11.7	10.4	NS	15.9	9.9	NS
Biochemical data									
Hemoglobin (g/dL)	13.9±1.6	13.2±1.7	NS	13.5±1.7	13.3±1.7	NS	12.7±1.8	13.8±1.6	<0.01
CrCl (Cockroft-Gault, ml/min/1.73m^2)	86.5±31.7	57.7±17.8	<0.001	71.2±29.2	60.8±20.7	0.001	40.1±7.0	78.5±23.7	<0.001
Anticoagulant treatment									
Prior use of VKA (%)	35.1	37.7	NS	34.8	45.9	0.02	40.6	35.7	NS
Dosage of rivaroxaban (%)* 15 mg 20 mg	20.8 79.2	65.4 34.6	<0.001	46.3 53.7	54.5 45.5	NS	74.8 25.2	39.6 60.4	<0.001

AF: atrial fibrillation; CrCl: creatinine clearance; VKA: vitamin K antagonists: DOACs: direct oral anticoagulants;TIA: transient ischemic attack.

Table 4. Thromboembolic and bleeding events according to age, prior stroke/TIA and renal function.

Variable	Age ≤75 years (n=289; 39.5%)	Age >75 years (n=443; 60.5%)	P	No prior stroke/TIA (n=605; 83.2%)	Prior stroke/TIA (N= 122; 16.8%)	P	CrCl<50 ml/min/1.73m^2 (N= 180; 24.6%)	CrCl ≥50 ml/min/1.73 m^2 (N=552; 75.4%)	P
Death, % (events per 100 patient-years) No cardiovascular Cardiovascular	4.5 (2.3) 3.1 (1.6) 1.4 (0.7)	14.7 (7.8) 8.2 (4.4) 6.5 (3.4)	<0.001 <0.01 <0.01	9.1 (4.8) 5.7 (3.0) 3.4 (1.8)	18.9 (10,4) 12.0 (6.7) 6.9 (3.7)	0.003 0.01 NS	17.5 (9.5) 9.2 (5.0) 8.3 (4.5)	7.6 (3.9) 5.5 (2.9) 2.1 (1.0)	0.001 NS 0.001
Stroke, % (events per 100 patient-years)	0 .7 (0.4)	5.2 (2.8)	0.001	2.8 (1.5)	6.6 (3.6)	0.04	9.2 (5.0)	2.3 (1.2)	0.001
Nonfatal myocardial infarction, % (events per 100 patient-years)	1.4 (0.7)	2.5 (1.3)	NS	1.8 (0.9)	3.3 (1.8)	NS	2.8 (1.5)	1.4 (0.7)	NS
Intracranial bleeding, % (events per 100 patient-years)	0.3 (0.2)	0.9 (0.5)	NS	0.7 (0.4)	0.8 (0.4)	NS	0 (0)	1.1 (0.6)	NS
Major bleeding, % (events per 100 patient-years)	3.5 (1.8)	7.7 (4.1)	0.025	5.1 (2.7)	10.7 (5.9)	0.03	7.0 (3.8)	6.4 (3.3)	NS

CrCl: creatinine clearance; TIA: transient ischemic attack.

Figure 1. Proportion of patients with stroke according to CHA_2DS_2-VASc score.

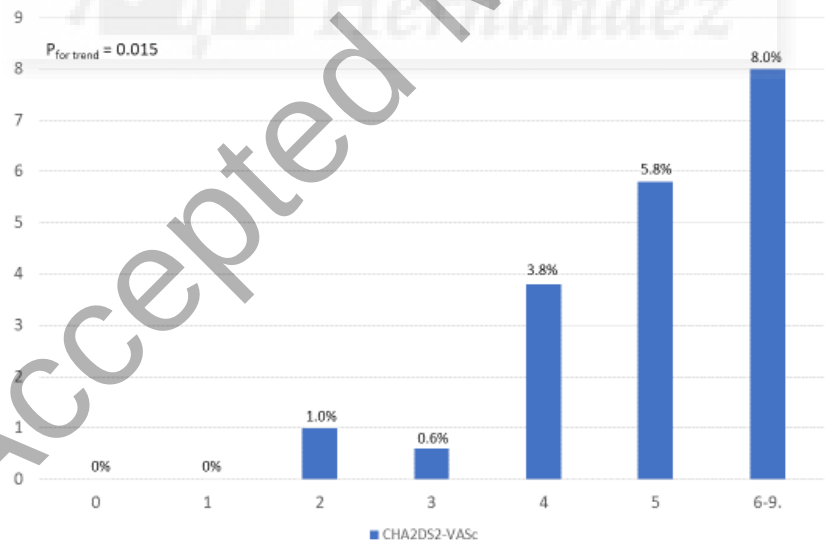


Figure 2. Proportion of patients with major bleeding according to HAS-BLED score.

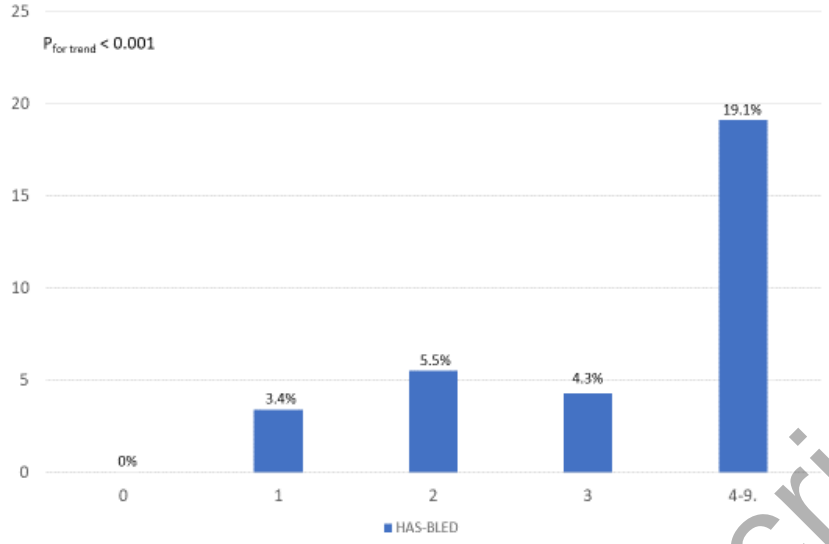
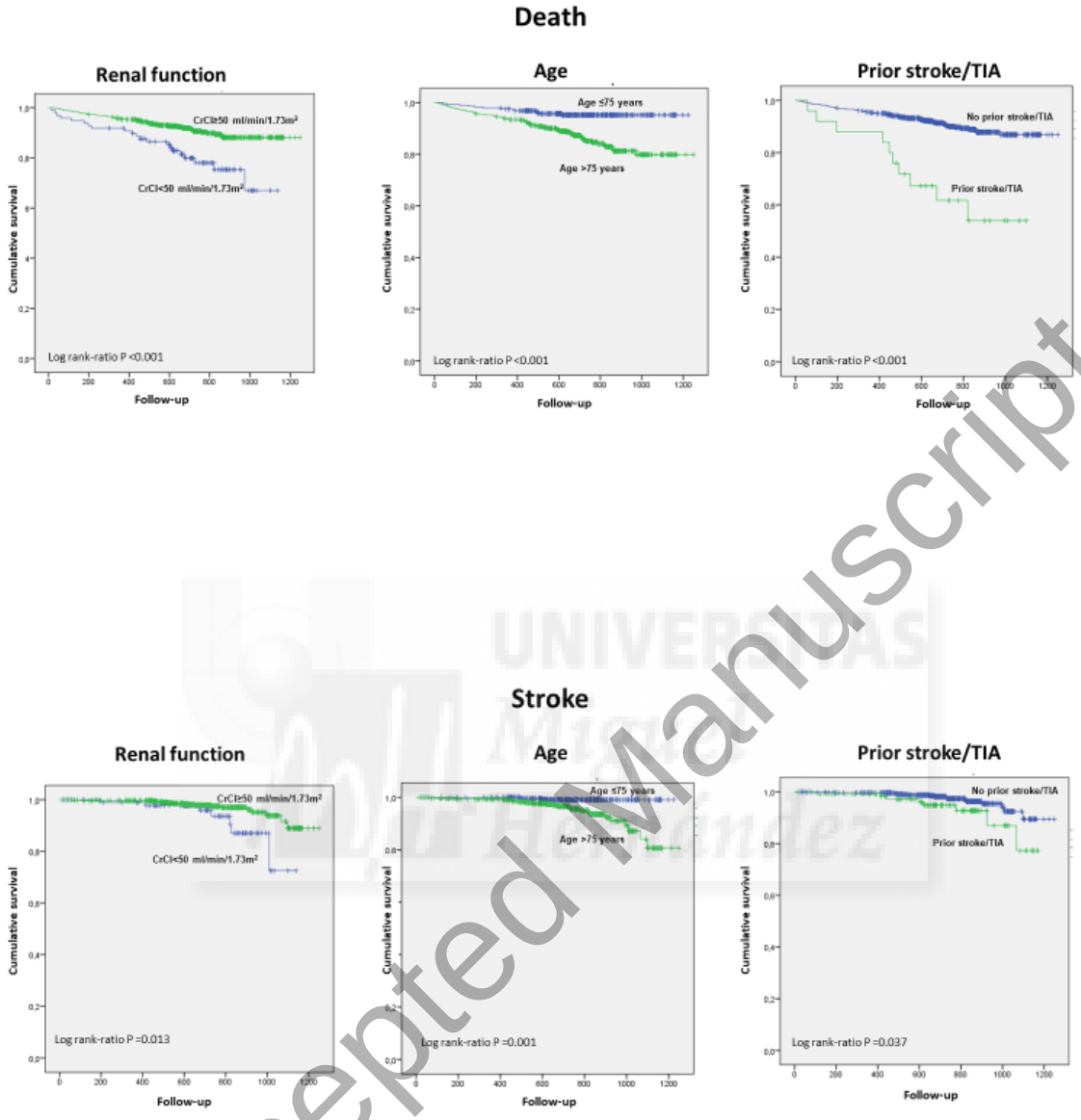
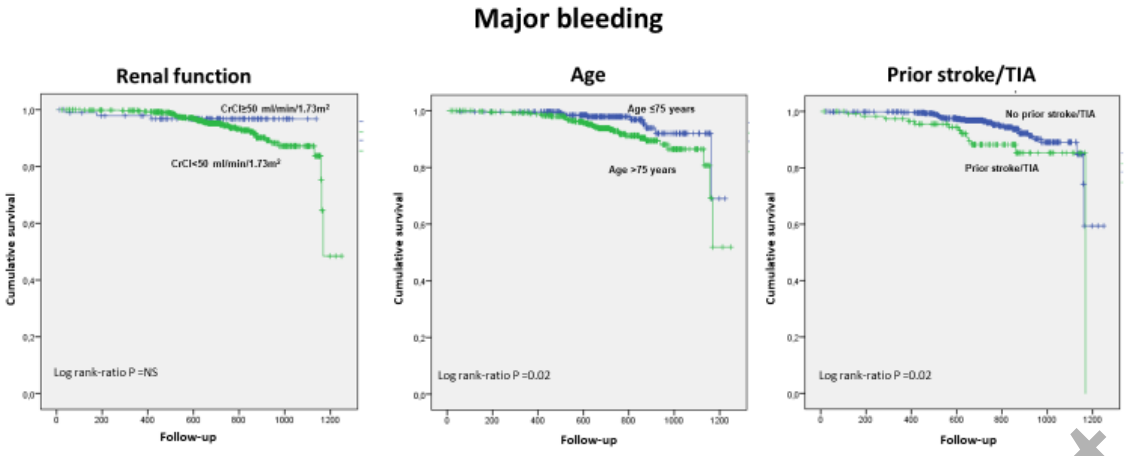


Figure 3. Kaplan-Meier curves of death, stroke and major bleeding, Thromboembolic and bleeding events according to age, prior stroke/TIA and renal function.





CrCl: creatinine clearance; TIA: transient ischemic attack.

Anexo. Comunicación SEC 2018

Rev Esp Cardiol. 2018;71(Supl 1):227

REVISTA ESPAÑOLA DE CARDIOLOGIA

7004-10 - EFECTIVIDAD, SEGURIDAD Y DOSIFICACIÓN DE RIVAROXABÁN EN UNA COHORTE DE 732 PACIENTES CON FIBRILACIÓN AURICULAR NO VALVULAR

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Resumen

Introducción y objetivos: El objetivo del estudio fue evaluar el perfil clínico, la efectividad y la seguridad de rivaroxabán en la práctica clínica.

Métodos: Estudio retrospectivo de pacientes con fibrilación auricular no valvular (FANV), que iniciaron tratamiento anticoagulante con rivaroxabán para la prevención del ictus entre diciembre de 2012 y diciembre de 2015 en 2 hospitales terciarios en España. Los pacientes fueron seguidos hasta febrero de 2018, registrándose eventos clínicos adversos en el 99,7% de los mismos.

Resultados: Se incluyeron 732 pacientes en total. La edad media fue de 76,4 ± 9,2 años (60,5% > 75 años), el 54,5% eran mujeres, y el 46,6% tenían FA permanente. Con respecto al riesgo tromboembólico y hemorrágico, el CHA_2DS_2-VASc medio fue 3,9 ± 1,5 (95,5% ≥ 2) y el HAS-BLED medio 2,3 ± 0,9 (38,3% ≥ 3), respectivamente. La presencia de factores de riesgo cardiovascular fue frecuente (hipertensión arterial 87,5%, diabetes 26,5%), así como de enfermedad vascular (ictus/ataque isquémico transitorio 16,8%, insuficiencia cardiaca 14,7%, cardiopatía isquémica 11,3%, enfermedad arterial periférica 3,2%). El 24,6% de los pacientes tenían un aclaramiento de creatinina (Cockroft-Gault) < 50 ml/min y el 5,6% antecedentes de sangrado mayor. Con respecto al tratamiento anticoagulante, el 36,6% de los pacientes había sido previamente anticoagulado con antagonistas de la vitamina K, el 1,5% con otro anticoagulante oral directo, y el resto (61,9%), se inició con rivaroxabán. Las dosis de rivaroxabán prescritas fueron 20 mg (53,3%) y 15 mg (47,7%). En los pacientes con aclaramiento de creatinina ≥ 50 ml/min/1,73 m^2 estos porcentajes fueron 60,4% y 39,6%, respectivamente, y en los sujetos con un aclaramiento < 50 ml/min/1,73 m^2 25,2% y 74,8%, respectivamente. En la tabla se resumen los eventos tromboembólicos y hemorrágicos. Dentro de los sangrados mayores, el 47,7% fueron de origen gastrointestinal, el 13,6% hematoma, y el 11,4% intracraneal.

Eventos tromboembólicos y hemorrágicos	
Seguimiento medio (meses)	22,7 ± 7,4

Muerte, % (eventos por 100 pacientes-año)	10,7 (5,6)
Cardiovascular	3,8 (2,0)
Sangrado	0,7 (0,4)
Ictus	0,4 (0,05)
Ictus, % (eventos por 100 pacientes-año)	3,4 (1,8)
Infarto de miocardio, % (eventos por 100 pacientes-año)	2,0 (1,0)
Sangrado intracraneal, % (eventos por 100 pacientes-año)	0,7 (0,4)
Sangrados mayores, % (eventos por 100 pacientes-año)	6,0 (3,2)
Sangrados menores, % (eventos por 100 pacientes-año)	15,4 (8,1)

Conclusiones: En nuestro medio, los pacientes tratados con rivaroxabán tienen una edad avanzada y un elevado riesgo tromboembólico. La dosificación de rivaroxabán de acuerdo a la ficha técnica es mejorable en un porcentaje significativo de pacientes. Las tasas de complicaciones tromboembólicas y hemorrágicas con rivaroxabán en este tipo de pacientes tratados en la práctica clínica, ofrecen datos superponibles a los registros internacionales.

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