Safety of oral anticoagulants in advanced chronic kidney disease

JULIANA MARCELA BUSTAMANTE-TRESPALACIOS, MARÍA CRISTINA URIBE-BARRADA, SUSANA CASTRO-SÁNCHEZ, JUAN CARLOS ARRIETA-BECHARA • MEDELLÍN (COLOMBIA).

DOI: https://doi.org/10.36104/amc.2021.1945

Abstract

Background: patients who take long-term oral anticoagulants and also have CKD have a greater probability of bleeding.

Methods: a retrospective, descriptive cohort study reviewing the clinical charts of anticoagulated patients with Stage 3 CKD or above seen at an anticoagulation clinic, in order to evaluate hemorrhagic events and baseline characteristics of the population over a two-year period.

Results: 238 patients were included. The anticoagulants used were warfarin (45%), rivaroxaban (31.5%), apixaban (14.3%) and dabigatran (3.4%). According to the KDIGO classification, 78% of the patients had CKD G3 (37.3% G3a and 40.7% G3b), 15.9% G4 and 5.8% G5 with renal replacement therapy (RRT). During the study period, only 20 patients (8.4%) had hemorrhagic events; of these, seven (35%) were major (four associated with warfarin, two with rivaroxaban and one with apixaban). The other 13 bleeds were minor and associated with warfarin in 46.1% of the cases. Gastrointestinal bleeding was the most common (35%), followed by soft tissues (30%). There was only one fatal bleed, which occurred in the central nervous system (CNS) in a patient with CKD G4.

Conclusion: a low rate of bleeding was found, which could be related to close follow up by an anticoagulation clinic. The anticoagulant most frequently associated with bleeding was warfarin, which could be related to a low time in therapeutic range (48.8%). Due to the low rate of events, comparisons could not be made. (Acta Med Colomb 2021; 46. DOI: https://doi.org/10.36104/amc.2021.1945).

Key words: *anticoagulants, chronic renal failure, major bleeding, minor bleeding, safety, hemorrhage, warfarin, apixaban, rivaroxaban, dabigatran.*

Dras. Juliana Marcela Bustamante-Trespalacios y María Cristina Uribe-Barrada: Residentes de Medicina Interna; Susana Castro-Sánchez: Estudiante de Medicina; Dr. Juan Carlos Arrieta-Bechara: Médico Internista y Vascular. Profesor de Medicina Vascular. Director Laboratorio Vascular y Director Clínica de Anticoagulación de la IPS Universitaria Universidad de Antioquia. **Universidad de Antioquia**. Medellín (Colombia).
Correspondencia: Dra. María Cristina Uribe-Barrada. Medellín (Colombia).
E-Mail: crysuriba@gmail.com
Received: 12/VII/2020 Accepted: 01/III/2021

Introduction

Direct oral anticoagulants (DOACs) emerged in response to the search for an ideal anticoagulant, after warfarin had been the only available anticoagulant for a long time (1, 2). The DOACs like rivaroxaban, apixaban, dabigatran, edoxaban and betrixaban (the first three of these available on the Colombian market), are widely recommended for their proven efficacy and greater safety when compared in patients with nonvalvular atrial fibrillation (AF) (3-6).

Warfarin is a medication directly related to hemorrhagic adverse events, with an estimated 3% frequency of major and fatal bleeding at three months (7), which could be higher in our setting due to lack of adherence to treatment, difficulties in patient education, irregular follow up and a low percentage of time in therapeutic range (TTR) (2, 8). In contrast, DOACs have proven to have advantages over warfarin, like rapid onset of action, a predictable effect, low interindividual variability, few drug interactions, improved adherence, decreased hospitalization costs, and no need for periodic monitoring and frequent dose adjustments, along with decreased major bleeding as a fundamental safety outcome (9, 10).

From a pharmacokinetics perspective, these medications are known to differ substantially in oral bioavailability, plasma protein binding and renal excretion (11, 12). The latter is higher for dabigatran (80%), while with edoxaban, rivaroxaban, apixaban and betrixaban, 50, 33, 27 and 11% of the dose is excreted unchanged, respectively (3, 13-15).

It is common to find patients with an indication for anticoagulation in daily medical practice, mainly due to atrial fibrillation (AF), and many of these have chronic kidney disease (CKD) (16, 17). Thus, conventional treatment must be studied to see if it is equally valid for this specific population.

The large, randomized trials which have evaluated the effectiveness and safety of direct anticoagulants vs. warfarin have, in general, excluded patients with advanced CKD and on dialysis, and therefore their treatment is currently contro-

versial (18-21). So far, only observational studies with small sample sizes (22-24) and pharmacologically based studies are available as the sole support for making complex medical decisions, but we still do not know if they are the best decisions for the patients and the healthcare system. Thus, the objective of this paper is to describe the sociodemographic, clinical and laboratory characteristics of anticoagulated individuals with advanced CKD in stages 3, 4 and 5 at IPS Universitaria Universidad de Antioquia in the city of Medellín (Colombia), and to report the cases of minor, major and fatal hemorrhage which occurred.

Materials and methods

Study design

This is a descriptive, retrospective cohort study on the safety of anticoagulants in patients with stage 3, 4 and 5 CKD.

Location

From January 2017 to December 2018, the medical charts of anticoagulated patients seen in the outpatient program of the institution's "anticoagulation clinic" were followed.

Participants

The inclusion criteria were: patients over the age of 18 with a prior diagnosis of CKD made by the attending physician or with creatinine clearance < 60 mL/min/1.73 m^2 on two consecutive measurements at least three months apart, and who required anticoagulation for at least three months.

Patients without a clear diagnosis or without a known indication for anticoagulation, those who only had an abnormal creatinine level on follow up, and patients who were not able to be seen a minimum of two times at least three months apart, were excluded.

Variables

The analyses included variables such as: sex; age; type of health insurance; indication for anticoagulation; anticoagulant and, if warfarin, INR at each visit and when bleeding, as well as TTR. The CKD stage, comorbidities and medications taken prior to anticoagulation were also included, along with major or minor bleeding, the affected organ, need for transfusion, GFR and comorbidities. Functional class was determined according to the medical chart report.

Chronic kidney disease is defined as the presence of abnormal kidney structure or function for at least three months, with health repercussions. Any of the following markers of kidney damage should be present for three months: elevated albuminuria, urinary sediment abnormalities, electrolyte abnormalities or other tubular dysfunctions, histological structural abnormalities, structural abnormalities on imaging tests, kidney transplantation or evidence of GFR < 60 mL/min/1.73 m^2 (25). (The more than three-month duration of some of these abnormalities was determined based on the medical chart.)

The kidney disease stage was assessed through serum creatinine calculation using the CKD Epidemiology Collaboration (CKD-EPI) formula, as recommended by the 2012 KDIGO guidelines (25) and based on GFR, as follows: normal (G1) GFR > 90 mL/min/1.73 m^2, G2: 60-80 mL/min/1.73 m^2, G3a: 45-59 mL/min/1.73 m^2, G3b: 30-44 mL/min/1.73 m^2, G4: 15-29 mL/min/1.73 m^2 and G5: <15 mL/min/1.73 m^2.

The International Society on Thrombosis and Haemostasis (ISTH) criteria were used to assess bleeding (26).

Major bleeding: clinically evident bleeding which meets one of the following criteria:

- Hemorrhage resulting in a fall in hemoglobin level of 2 g/dL or more for a 24-hour period.
- Bleeding which requires the transfusion of two or more units of packed red blood cells.
- Bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome or retroperitoneal).
- Bleeding leading to death.

Minor bleeding: a clinically evident hemorrhagic event which does not meet any of the previous criteria for major bleeding but leads to:

- Hospital admission for hemorrhage.
- Physician-guided medical or surgical treatment for bleeding.
- A change in antithrombotic therapy.

Fatal bleeding: defined as a hemorrhagic event that is the main cause of death or directly contributes to death.

Source of the data

The anticoagulation clinic database and medical charts of IPS Universitaria Universidad de Antioquia.

Biases

Due to the descriptive nature of the study, there are biases related to the lack of patient randomization. The population's lack of representativeness is also implicit, along with some missing data in the medical charts. To control the biases, the medical charts of different specialists were evaluated on random dates and during appointments at the anticoagulation clinic.

Sample size

Since this was a descriptive study, sample size was not calculated and, for convenience, all patients seen during the study period were selected. Out of 1,338 patients seen in the anticoagulation clinic, 238 medical charts which met the mentioned inclusion criteria were analyzed.

Statistical methods

Nominal variables are presented as absolute and relative frequencies. Continuous variables are presented using averages and standard deviation. The only missing value in the medical chart data was race, which was assumed to be "not African American" for all patients, in order to apply the CKD-EPI formula to obtain the GFR.

The Rosendaal method was used to calculate TTR.

The database was created using the Excel 2017 (Microsoft Corp.) program, and IBM SPSS Statistics 20 statistical software was used for analysis.

The project was presented to IPS Universitaria Universidad de Antioquia and was studied and approved by this institution's Ethics and Research Committee. Bioethical principles were taken into account in the conduction of this study; results were obtained without violating patients' rights and with the objective of improving understanding of the diseases for the benefit of the affected population and medical research. As it was a descriptive study, informed consent was not obtained from the patients.

Results

A total of 7,267 care encounters were recorded in the anticoagulation clinic´s database between January 2017 and December 2018. After removing duplicate records, 1,338 medical charts were reviewed to select those which met the inclusion criteria, for a total of 238 patients (Figure 1).

The main reason for anticoagulation was AF (81.9%), followed by venous thromboembolic disease both in lower limbs and the lungs (7.6%). The most frequent age group was 81-90 years (39.1%), the sex distribution was similar with 52.1% women and 47.9% men, and 65.5% had contributive and 34.5% had subsidized health insurance.

The most frequently used anticoagulant was warfarin (45%), followed by rivaroxaban (31.5%) and apixaban (14.3%). A total of 36 patients changed anticoagulant during follow up (Table 1).

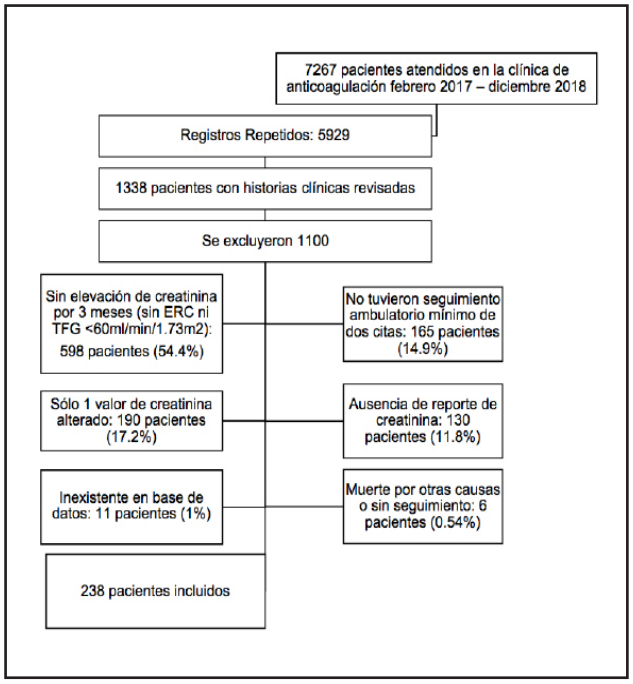

Figure 1. *Flowchart showing the participant selection process.*

Table 1. *Description of the patients' baseline characteristics.*

Characteristics (n=238)		#	%
Sex	Male	114	47.9
	Female	124	52.1
Age	40-50	3	1.3
	51-60	12	5.0
	61-70	31	13.0
	71-80	78	32.8
	81-90	93	39.1
	>91	21	8.8
Health insurance	Subsidized	82	34.5
	Contributive	156	65.5
Indications for anticoagulation	Atrial fibrillation	195	81.9
	Venous thromboembolic disease	18	7.6
	Atrial flutter	8	3.4
	Mechanical heart valve	6	2.5
	Thrombus in a heart chamber	6	2.5
	Other	4	1.7
	Biological heart valve + AF	1	0.4
Anticoagulant	Warfarin	107	45.0
	Rivaroxaban	75	31.5
	Apixaban	34	14.3
	Enoxaparin + warfarin	12	5.0
	Dabigatran	8	3.4
	Dalteparin + warfarin	2	0.8
Comorbidities	Heart failure	126	52.9
	Hypertension	174	73.1
	Pulmonary disease	97	40.8
	Diabetes mellitus	81	34.0
	Thyroid disease	74	31.1
	Coronary disease	63	26.5
	Aneurysms	10	4.2
	Gastric ulcer	6	2.5
	Cirrhosis	6	2.5
	Carotid disease	5	2.1
	Systemic lupus erythematosus	4	1.7
	Cancer	4	1.7
	Esophageal varices	2	0.8
	None	2	0.8
Medications	IBP	95	39.9
	ASA	24	10.1
	Ranitidine	10	4.2
	Anticonvulsants	7	2.9
	Amiodarone	5	2.1
	Antibiotics	1	0.4
	Antitubercular medications	1	0.4
	Gemfibrozil	1	0.4
	NSAIDS	0	0.0
	None	0	0.0
	Others	116	48.7

Table 2. *Stage of chronic kidney disease and bleeding occurrence.*

	Total patients		Patients with bleeding	
	Number (n=238)	%	Number (n=20)	%
3a	89	37.3	11	55.0
3b	97	40.7	4	20.0
4	38	15.9	3	15.0
5 - renal replacement therapy	14	5.8	2	10.0

The average TTR in patients on warfarin was 48.8% and the median was 51% (0-100% for minimum and maximum values, respectively).

The majority of patients were in stage G3a (37.3%) and G3b (40.7%) CKD, and the greatest frequency of bleeding was in this stage. There were only 5.8% in G5 and, of these, 100% were on renal replacement therapy (Table 2).

Out of all the patients studied, bleeding was seen in 20 (8.4%), and of these, 7 (35%) had major bleeding. Warfarin was the anticoagulant associated with 50% of these cases, followed by rivaroxaban (20%) and apixaban and dabigatran (15% each). The most frequent site of major bleeding was the digestive tract (five patients); there was only one case of fatal bleeding in a 95-year-old patient with stage 3b kidney disease who was receiving apixaban and had a seizure, moderate head trauma and central nervous system (CNS) bleeding. The remaining hemorrhages were minor (13 patients); 46.1% were due to warfarin and 15% to dabigatran. The most common site for these bleeds was soft tissues (30%).

Of the 10 patients who bled on warfarin, six had subtherapeutic INRs, three had an INR in the 2-3 range and one had an INR less than 2.0 (Table 3).

The description of each of the subjects who bled is shown in Table 4.

Discussion

This study described stage 3, 4 and 5 CKD patients who were seen at the anticoagulation clinic at IPS Universitaria Universidad de Antioquia in Medellín, Colombia over a period of two years.

It is common to find patients with an indication for anticoagulation in daily clinical practice, due to the high prevalence of AF which increases with age, being approximately 2.3% at age 40, and greater than 6% in those over 65 (27). Furthermore, CKD, with a prevalence of approximately 12% in the general population (2 per 100 population in Colombia) in 2014 (28), has been defined as an independent cardiovascular risk factor as it has been pathophysiologically related to both thrombotic and hemorrhagic events (29, 30).

Approximately one out of every five patients with CKD has AF, which is 2-3 times more than in the population without CKD (31). For those on peritoneal dialysis, the prevalence is up to 7%, and for hemodialysis, it is 13%. The percentage of patients with AF and CKD also increases with

Table 3. *Analysis of hemorrhagic events according to type of bleeding: major or minor.*

	Major bleeding (n=7)		Minor bleeding (n=13)	
Total patients (n=20)	#	%	#	%
Sex				
Male	5	25.0	11	55.0
Female	2	10.0	2	10.0
Type of bleeding				
Nonfatal	6	30.0	13	65.0
Fatal	1	5.0	0	0.0
Age (years)				
51 to 60	1	5.0	2	10.0
61 to 70	1	5.0	0	0.0
71 to 80	2	10.0	5	25.0
81 to 90	2	10.0	4	20.0
Over 90	1	5.0	2	10.0
Type of Health Insurance				
Contributive	4	20.0	10	50.0
Subsidized	3	15.0	3	15.0
Reason for anticoagulation				
Atrial fibrillation	6	30.0	11	55.0
Venous thromboembolic disease	0	0.0	2	10.0
Mechanical heart valve	1	5.0	0	0.0
Anticoagulant				
Warfarin	4	20.0	6	30.0
INR > 3.0	1	5.0	5	25.0
INR 2-3	2	10.0	1	5.0
INR < 2	1	5.0	0	0.0
Rivaroxaban	2	10.0	2	10.0
Apixaban	1	5.0	2	10.0
Dabigatran	0	0.0	3	15.0
Kidney disease stage				
3a	4	20.0	7	35.0
3b	1	5.0	3	15.0
4	1	5.0	2	10.0
5	1	5.0	1	5.0
Affected site				
Gastrointestinal	5	25.0	3	15.0
Genitourinary	1	5.0	3	15.0
Central nervous system	1	5.0	0	0.0
Soft tissues	0	0.0	6	30.0
Nasal - oral mucosa	0	0.0	2	10.0
Transfusions				
YES	3	15.0	0	0.0
NO	4	20.0	13	65.0

Table 4. *Description of patients who had bleeding.*

#	Type of bleeding	Sex	Age (years)	Health insurance	Fatal	Site of bleeding	GFR ml/ min/1.73 m2	Anticoagulant	INR	Transfusion	Reason for anticoagulation	Comorbidities
1	Minor	M	87	C	No	Gastrointestinal	40.10	Warfarin	3.2	No	Nonvalvular AF	Pulmonary disease, HTN
2	Minor	M	80	C	No	Gastrointestinal	58	Warfarin	3.2	No	Nonvalvular AF	HTN, pulmonary disease, hypothyroidism, heart failure.
3	Minor	M	85	C	No	Soft tissues	56.90	Dabigatran	NA	No	Nonvalvular AF	HTN, dyslipidemia, heart failure, hypothyroidism, dementia.
4	Minor	M	77	C	No	Genitourinary	33.30	Apixaban	NA	No	Nonvalvular AF	SLE, hypothyroidism, HTN, pulmonary disease.
5	Minor	M	94	C	No	Genitourinary	21.60	Dabigatran and ASA	NA	No	Nonvalvular AF	CVA, heart failure, DM2, HTN, hypothyroidism, prostatic hyperplasia
6	Minor	M	71	C	No	Soft tissues	46.00	Warfarin	2.5	No	Nonvalvular AF and intramural thrombus	Heart failure with implantable cardioverter defibrillator
7	Minor	F	87	C	No	Soft tissues	51.00	Dabigatran	NA	No	Nonvalvular AF and chronic PTE	Pulmonary disease
8	Minor	M	94	C	No	Soft tissues	40.70	Rivaroxaban	NA	No	Nonvalvular AF	HTN, heart failure, pulmonary disease
9	Minor	F	73	C	No	Gastrointestinal	55.80	Apixaban	NA	No	VTED	HTN, dyslipidemia, osteoporosis, pulmonary disease
10	Minor	M	53	C	No	Genitourinary	TRR	Rivaroxaban	NA	No	VTED	SCI, neurogenic bladder and urinary catheter, HTN, DM2, epilepsy.
11	Minor	M	54	S	No	Soft tissues Nasal mucosa	22.30	Warfarin	4.3	No	Nonvalvular AF	HTN, heart failure with a cardiac resynchronization device, hepatic cirrhosis
12	Minor	M	79	S	No	Soft tissues Oral mucosa	45.90	Warfarin	8.8	No	Nonvalvular AF	HTN, DM2
13	Minor	M	87	S	No	Nasal mucosa	38.20	Warfarin	6.6	No	Nonvalvular AF	HTN, dual chamber pacemaker for atrioventricular block, heart failure
14	Major	M	68	S	No	Gastrointestinal Nasal mucosa	55.70	Warfarin	8.2	Yes	Nonvalvular AF/flutter	Heart failure, pulmonary disease, HTN
15	Major	M	54	S	No	Gastrointestinal	TRR	Warfarin	1.73	Yes	Nonvalvular AF and atrial thrombus	HTN, recurrent soft tissue sepsis due to an arteriovenous fistula, peptic ulcer
16	Major	F	82	S	No	Gastrointestinal	59.00	Rivaroxaban	NA	No	Nonvalvular AF	HTN, heart failure
17	Major	M	95	C	Yes	Central nervous system (trauma)	28.06	Apixaban	NA	No	Nonvalvular AF	Heart failure and coronary disease, pulmonary disease, diverticular disease and hypothyroidism.
18	Major	F	79	C	No	Gastrointestinal	28.40	Warfarin	2.2	No	Nonvalvular AF	Heart failure, pulmonary disease, HTN, hypothyroidism, diverticular disease and gastric ulcer
19	Major	M	82	C	No	Gastrointestinal	59.00	Rivaroxaban	NA	Yes	Nonvalvular AF	HTN, heart failure, cardiac resynchronization device, pulmonary disease
20	Major	M	68	C	No	Genitourinary	49.60	Warfarin	2.43	No	Mechanical aortic valve	CVA with neurogenic bladder, prostatic hyperplasia, HTN, pulmonary disease

M: male, F: female, C: contributive, S: subsidized, AF: atrial fibrillation, VTED: venous thromboembolic disease, HTN: hypertension, DM2: diabetes mellitus 2, CVA: cerebrovascular accident, SCI: spinal cord injury, NA: not applicable, RRT: renal replacement therapy, ASA: acetylsalicylic acid.

age (32). Our study showed that 51.7% of the patients were over the age of 70.

According to the literature, AF is the most common reason for anticoagulation in patients with CKD. In our study it accounted for 81.5% of the patients, similar to the findings of international reports (33, 34).

With regard to the safety of anticoagulants, a study performed in Canada with 1,626 patients on hemodialysis who took warfarin yielded an adjusted HR for bleeding of 1.44 (95%CI: 1.13-1.85), and the authors suggest that the risk-benefit profile does not support the routine use of warfarin to reduce cerebrovascular accidents in patients on hemodialysis (35). A meta-analysis in 2007 found that those with terminal CKD who were treated with warfarin had a 10 times greater risk of major bleeding than the general population and that these events occurred even when the INR was between 1.5 - 2.0 (36). In our study, out of 107 patients on warfarin, 10 bled (9.34%); of these, only two were using ASA and not all were overanticoagulated at the time of bleeding. There was a 5.6% rate of minor bleeding and 3.7% rate of major bleeding, which is lower than that of Kooiman et al.'s (2014) study which reported 15.6% for the latter type of bleeding, keeping in mind that the sample in this study was larger (n=724) (37). This study also reported bleeding in patients with INRs within the therapeutic range, which was found in our study (two patients with major bleeding and one with minor bleeding).

Despite the greater proven safety of DOACs, in our study we found that warfarin was the most commonly used medication (45.0%), even though 65.5% of the patients had contributive health insurance. This could lead us to question the reason for choosing warfarin over the rest of the anticoagulants and to consider whether the weight of evidence in the Colombian population is sufficient for choosing the type of anticoagulant, or if social, economic and cultural factors have a greater weight when prescribing them.

An important outcome for patients on warfarin is TTR, which estimates the percentage of time during which the INR is within the desired treatment range, and is widely used as an indicator of anticoagulation monitoring (38). This study found a TTR of 48.8%, which means that for more than half the time, the patients were outside the target. This target failure is well described in the literature, such as by Chaaban et al. (2015) who presented data on the use of warfarin in patients on hemodialysis (HD) versus those with normal kidney function and found that not only did HD patients have more hemorrhages, but the INR was only within the therapeutic range 25% of the time in this group (39). Yang et al. (2017) recently published their study in which they found that only 21% of patients on dialysis had a TTR greater than 60%; in addition, they found that for 30% of the time, the INR was notably outside the range (INR less than 1.5 or greater than 3.5) (40). All of this makes anticoagulation with warfarin entirely unpredictable and creates the possibility of carrying out more studies on this topic, given that the population is different, possibly older, with serious associated illnesses and difficulties in accessing the healthcare system and adhering to treatment.

With regard to the DOACs, apixaban is approved at a dose of 5 mg twice a day, which needs to be adjusted to 2.5 mg every 12 hours for patients who meet two of the following criteria: creatinine greater than 1.5 mg/dL, over the age of 80, or weight under 60 kg, according to the ARISTOTLE study (41). This study excluded patients with a GFR less than 25 mL/min, and thus the population with stage 4 and 5 CKD is not well represented. In spite of this, the updated 2019 AHA guidelines for AF and the FDA recommend using apixaban for patients with advanced CKD, including those on hemodialysis (42). This continues to be controversial because the recommendation is based on a pharmacodynamics study with 16 patients and a US Medicare register, and therefore the quality of the scientific evidence is not the best (43, 44). In 2019, preliminary results of the RENAL-AF study were presented, comparing apixaban vs. warfarin on dialysis. The study was not conclusive, as it did not achieve the expected enrollment and thus was stopped before the stipulated time. In addition, the TTR for patients on warfarin was 44%, with a large proportion of patients in the subtherapeutic range (45). Our study showed that out of 34 patients on apixaban, three had bleeding (a rate of 8.8%). One of these was the only case of fatal bleeding; however, it was associated with head trauma which was the cause of death, this patient was elderly, and he had a GFR of 28 mL/min and therefore had an adjusted medication dose.

Likewise, rivaroxaban, in its main study (ROCKET-FA), excluded GFR < 30 mL/min (46). There are observational and pharmacological studies which demonstrate the safety of rivaroxaban in stage G4 CKD, and therefore it is approved in the United States for this indication, while other countries like Canada only use its traditional recommendation (47, 48). In our study, 4 out of 75 subjects on rivaroxaban had bleeding (a 5.3% rate of bleeding) and all of these were in stage 3 CKD, except for one who required temporary renal replacement therapy.

Dabigatran is contraindicated for patients with GFR < 15 mL/min, according to international guidelines, but are there are no studies with large numbers of patients even for stage 4 CKD. Our study shows that this medication had the highest rate of bleeding (37.5%). Therefore, taking into account its high rate of renal excretion, we consider that it is not the drug of choice in patients with CKD (49). Even so, it is approved by the FDA for an adjusted dose of 75 mg every 12 hours based on a pharmacological prediction model (50).

The efficacy of oral anticoagulants has been very well established in controlled studies and more information is needed on their safety in different populations. This study described the clinical profiles and hemorrhagic events of anticoagulated individuals during follow up by IPS Universitaria Universidad de Antioquia from January 2017 to December 2018. This study represents the largest cohort

published to date of patients with chronic kidney disease and the use of anticoagulants (both warfarin and DOACs) in Colombia and Latin America.

The limitations of the current study are related to its retrospective nature, data collection and the absence of some data. Calculating the glomerular filtration rate using the CKD-EPI equation has some limitations given that race was not recorded for the vast majority of patients. The population in stage G5 CKD was scant. Neither CHADs2Vasc nor HAS-BLED were considered for interpreting the results for patients with AF.

Conclusion

The most common reason for anticoagulation was AF and the most frequent kidney disease stage was G3. Overall, there was a low rate of major bleeding, which could be related to close follow up at an anticoagulation clinic. This type of bleeding was more frequent in patients on warfarin, which was associated with a low TTR (48.8%). The safest medications were apixaban and rivaroxaban with adjusted doses.

The number of patients in stage G5 CKD was very low, and therefore conclusions cannot be drawn regarding this particular group.

Randomized clinical trials are needed to determine the safest anticoagulation strategy in this population.

Acknowledgements

To all the healthcare, administrative and research staff at the anticoagulation clinic at IPS Universitaria Universidad de Antioquia for the availability of the information and data collection.

References

1. **Turagam MK1, Parikh V2, Afzal MR2, et al.** Replacing warfarin with a novel oral anticoagulant: Risk of recurrent bleeding and stroke in patients with warfarin ineligible or failure in patients with atrial fibrillation (The ROAR study*). J Cardiovasc Electrophysiol*. 2017; 28(8):853-861
2. **Munir Pirmohamed, M**. Warfarin: almost 60 years old and still causing problems. *Br J Clin Pharmacol*. 2006; 62(5): 509–511.
3. **Kumar S, De Lusignan S, McGovern A, Correa A, Hriskova M, Gatenby P, et al**. Ischaemic stroke, haemorrhage, and mortality in older patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: A population based study from UK primary care. *BMJ*. 2018;360:1–10.
4. **Jaramillo Salamanca RG, Jiménez Gómez JD, Pinilla Roa AE.** Uso de los anticoagulantes orales directos en la práctica clínica. *Rev Fac Med*. 2016;64(2):295.
5. **Harel Z, Sholzberg M, Shah PS, Pavenski K, Harel S, Wald R, et al.** Comparisons between novel oral anticoagulants and vitamin K antagonists in patients with CKD. *J Am Soc Nephrol*. 2014;25(3):431–42.
6. **Harel Z, Sood MM, Perl J.** Comparison of novel oral anticoagulants versus vitamin K antagonists in patients with chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2015;24(2):183–92.
7. **Meena Zareh, BS,Andrew Davis, BS,and Sean Henderson.** Reversal of Warfarin-Induced Hemorrhage in the Emergency Department. *West J Emerg Med*. 2011; 12(4): 386–392.
8. **Laverde, LP. Gómez, SE.Montenegro, AC. et al.** Experiencia de una clínica de anticoagulación. *Rev Colomb Cardiol* 2015;22(5):224-230
9. **Lega J-C, Bertoletti L, Gremillet C, Boissier C, Mismetti P, Laporte S.** Consistency of safety profile of new oral anticoagulants in patients with renal failure. *J Thromb Haemost* 2014; 12: 337–43.
10. **Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S.** Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. *Cochrane Database of Systematic Reviews* 2017; 11. Art. No.: CD011373.
11. **Padrini R.** Clinical Pharmacokinetics and Pharmacodynamics of Direct Oral Anticoagulants in Patients with Renal Failure. *Eur J Drug Metab Pharmacokinet*. 2019;44(1).
12. **Parker, K. Mitra, S. Tachi J.** Is anticoagulating haemodialysis patients with non-valvular atrial fibrillation too risky?. *British Journal of Haematology*. 2018; 181: 725–736
13. **Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuhara S**. New oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. *Cochrane Database Syst Rev*. 2014;2014(11).
14. **Ramagopalan S V., Stamp E, Sammon CJ, Besford M, Carroll R, Mehmud F, et al.** Renal function and oral anticoagulant treatment of incident non-valvular atrial fibrillation: A retrospective study. Future Cardiol. 2019;15(4):301–9.
15. **Sardar P, Chatterjee S, Herzog E, Nairooz R, Mukherjee D, Halperin JL.** Novel oral anticoagulants in patients with renal insufficiency: A meta-analysis of randomized trials. *Can J Cardiol* [Internet]. 2014;30(8):888–97.
16. **R. Marinigh, D.A. Lane, G.Y.H. Lip,** Severe renal impairment and stroke prevention in atrial fibrillation, *J. Am. Coll*. Cardiol 2011; 57:1339–1348.
17. **Providencia R, Marijon E, Boveda S, Barra S, Narayanan K, Le Heuzey JY, Gersh BJ, Goncalves L.** Meta-analysis of the influence of chronic kidney disease on the risk of thromboembolism among patients with nonvalvular atrial fibrillation. *Am J Cardiol*. 2014;114(4):646–53.
18. **Hijazi Z., Hohnloser S.H., Oldgren J., et al.** Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation* 2014 129: 961–970.
19. **Manesh R. Patel, et al.** Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N Engl J Med* 2011; 365:883-891. DOI: 10.1056/NEJMoa1009638
20. **Granger, C. B.** Apixaban versus warfarin in patients with atrial fibrillation. *New Eng J Med* 2011; 365, 981–992. DOI: 10.1056/NEJMoa1107039
21. **Robert P. Giugliano, et al.** Edoxaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2013; 369: 2093-2104
22. **Lega JC, Bertoletti L, Gremillet C, Boissier C, Mismetti P, Laporte S.** Consistency of safety profile of new oral anticoagulants in patients with renal failure. *J Thromb Haemost*. 2014;12(3):337–43.
23. **Shin JI, Secora A, Caleb Alexander G, Inker LA, Coresh J, Chang AR, et al.** Risks and benefits of direct oral anticoagulants across the spectrum of GFR among incident and prevalent patients with atrial fibrillation. *Clin J Am Soc Nephrol*. 2018;13(8):1144–52.
24. **Hughes S, Szeki I, Nash MJ, Thachil J.** Anticoagulation in chronic kidney disease patients - The practical aspects. *Clin Kidney J*. 2014;7(5):442–9.
25. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012;2:337-414.
26. **Schulman S, Kearon C.** Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3: 692–4.
27. **Tan et al.** Warfarin use and stroke, bleeding and mortality risk in patients with end stage renal disease and atrial fibrillation: a systematic review and meta-analysis. *BMC Nephrology* (2016) 17:157. DOI:10.1186/s12882-016-0368-6
28. Cuenta de alto costo. Situación de la enfermedad renal crónica, hipertensión arterial y diabetes mellitus en Colombia. (Internet) (Consultado 2017 Dic 12) en Disponible en: https://cuentadealtocosto.org/site/images/Situaci%C3%B3n_de_la_Enfermedad_Renal_Cr%C3%B3nica_en_Colombia_2015.pdf.
29. **Wizemann V, Tong L, Satayathum S, et al.** Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney International* 2010; 77 (12):1098 – 1106. DOI: 10.1038/ki.2009.477
30. **Soliman EZ, Prineas RJ, Go AS, et al.** Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). *Am Heart J* 2010;159:1102-7.
31. **R. Marinigh, D.A. Lane, G.Y.H. Lip,** Severe renal impairment and stroke prevention in atrial fibrillation, *J. Am. Coll. Cardiol* 2011; 57:1339–1348. DOI:10.1016/j.jacc.2010.12.013.
32. **Providencia R, Marijon E, Boveda S, Barra S, Narayanan K, Le Heuzey JY, Gersh BJ, Goncalves L.** Meta-analysis of the influence of chronic kidney disease on the risk of thromboembolism among patients with nonvalvular atrial fibrillation. *Am J Cardiol*. 2014;114(4):646–53. DOI:10.1016/j.amjcard.2014.05.048
33. **Makani A, Saba S, Jain SK, Bhonsale A, Sharbaugh MS, Thoma F, et al.** Safety and Efficacy of Direct Oral Anticoagulants Versus Warfarin in Patients With Chronic Kidney Disease and Atrial Fibrillation. *Am J Cardiol* [Internet]. 2020;125(2):210–4. Available from: https://doi.org/10.1016/j.amjcard.2019.10.033

34. **Feldberg J, Patel P, Farrell A, Sivarajahkumar S, Cameron K, Ma J, et al**. A systematic review of direct oral anticoagulant use in chronic kidney disease and dialysis patients with atrial fibrillation. *Nephrol Dial Transplant*. 2019;34(2):265–77.
35. **Shah, M., Tsadok, M.A., Jackevicius, C.A., Essebag,V., Eisenberg, M.J., Rahme, E., Humphries, K.H., Tu, J.V., Behlouli, H., Guo, H. & Pilote, L.** Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. *Circulation* 2014; 129,1193–1203.
36. **Elliott, M.J., Zimmerman, D. & Holden, R.M**. Warfarin anticoagulation in hemodialysis patients: a systematic review of bleeding rates. *American Journal of Kidney Diseases* 2007; 50, 433–440. DOI: 10.1053/j.ajkd.2007.06.017
37. **Kooiman J, van Rein N, Spaans B, van Beers KA, Bank JR, et al.** Efficacy and safety of vitamin K-antagonists (VKA) for atrial fibrillation in non-dialysis dependent chronic kidney disease. *PLoS One*. 2014; 9;9(5):e94420.
38. **Miranda, H. Osorio, S. Giraldo, DP, et al.** Tiempo en rango terapéutico (TRT) en clínica de anticoagulación, Reportes de eventos adversos y factores asociados a bajo TRT. *Acta Médica Colombiana,* 2016; 41(1)
39. **Chaaban, A., Gebran, N., Abdelmegid, K., Abouchacra, S., Soliman, K., Agha, L. y Butt, L.** Effectiveness and safety of warfarin use for cardiac indications in hemodialysis patients. *Nephrology Dialysis Transplant* 2015; 30, 563–564.
40. **Yang, F., Hellyer, J.A., Than, C., Ullal, A.J., Kaiser, D.W., Heidenreich, P.A., Hoang, D.D., Winkelmayer, W.C., Schmitt, S., Frayne, S.M., Phibbs, C.S. y Turakhia, M.P.** Warfarin utilization and anticoagulation control in patients with atrial fibrillation and chronic kidney disease. *Heart* 2017; 103, 818–826. DOI: 10.1136/heartjnl-2016-309266
41. **Granger, C. B.** Apixaban versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine* 2011; 365, 981–992. DOI: 10.1056/NEJMoa1107039
42. **Society.January CT, et al.** 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm. *J Am Coll Cardiol*. 2019 Jan 21.
43. **Wang, X., Tirucherai, G., Marbury, T., Wang, T., Chang, M., Zhang, D., Song, Y., Pursley, J., Boyd, R. y Frost, R.** Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end stage renal disease on hemodialysis. *The journal of clinical Pharmacology,* 2016: 56 (5), 628-636. DOI:10.1002/jcph.628
44. **Siontis KC1,2, Zhang X3, Eckard A4, Bhave N1, et al.** Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States, *Circulation*. 2018;138(15):1519-1529.
45. RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF) Randomized Clinical Trial. AHA Congress 2019 (https://www.acc.org/latest-in-cardiology/clinical-trials/2019/11/15/17/29/renal-af).
46. **Manesh R. Patel, et al**. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N Engl J Med* 2011; 365:883-891. DOI: 10.1056/NEJMoa1009638
47. **Langas M, Moore K T.** Renal Impairment and Chronic Hemodialysis on the pharmacokinetics, pharmacodynamics and Safety of Rivaroxaban. *Journal of Renal Medicine* 2017; 1:2-9. DOI: http://www.imedpub.com/renal-medicine/
48. **Chan, K.E., Edelman, E.R., Wenger, J.B. et al.** Dabigatran and Rivaroxaban Use in Atrial Fibrillation Patients on Hemodialysis. *Circulation* 2015; 131(11): 972-979. DOI: 10.1161/CIRCULATIONAHA.114.014113.
49. **Knauf, F., Chaknos, M., Berns, J.S., Perazella, M.A**. Dabigatran and Kidney Disease: A Bad Combination. *Clin J Am Soc Nephrol* 2013 8:1591–1597. DOI: 10.2215/CJN.01260213
50. **Kooiman, J., Van der Hulle, T., Maas, H., Wiebe, S., Formella, S., et al**. Pharmacokinetics and Pharmacodynamics of Dabigatran 75 mg b.i.d. in Patients With Severe Chronic Kidney Disease. *Journal of the American College of Cardiology*. May 2016; 67 (20) 2442-2444; DOI: 10.1016/j.jacc.2016.03.516