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Vitamin K antagonists versus direct oral anticoagulants: Which is the best option for anticoagulation in kidney transplant recipients with atrial fibrillation?

Tânia de Brito Azevedo

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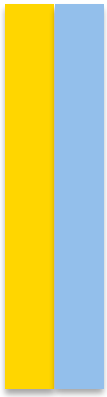

Vitamin K antagonists versus direct oral anticoagulants: Which is the best option for anticoagulation in kidney transplant recipients with atrial fibrillation?

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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RESUMO

Introdução: A fibrilação auricular é comum entre transplantados renais, e está associada a piores resultados clínicos, como a mortalidade e eventos tromboembólicos. No entanto, a eficácia e segurança dos antagonistas da vitamina K e dos anticoagulantes orais diretos em doentes transplantados renais não está ainda estabelecida, e as guidelines não fazem recomendações sobre este tópico, nem os scores de risco CHA_2DS_2-VASc e HAS-BLED estão validados para esta população. O objetivo deste estudo é avaliar o risco/benefício da anticoagulação oral em doentes transplantados renais com fibrilação auricular, e a eficácia dos scores em prever eventos tromboembólicos e hemorrágicos.

Métodos: Estudo de coorte retrospetivo, que incluiu doentes submetidos a transplante renal desde 2005 a 2020, com o diagnóstico de fibrilação auricular após a transplantação, sem presença concomitante de prótese valvular ou stent. Foram obtidas as caraterísticas demográficas e clínicas, assim como a estratégia de hipocoagulação, eventos tromboembólicos e hemorrágicos ocorridos, e a mortalidade. Foi usado o método de Kaplan-Meier com teste log-rank para comparar a sobrevida global e tempo livre de eventos tromboembólicos e hemorrágicos entre as estratégias de hipocoagulação. Comparamos também a percentagem de complicações de acordo com o estadio da doença renal crónica usando o teste exato de Fisher e o método de Kaplan-Meier com teste log-rank. Para avaliar o desempenho dos scores de risco CHA_2DS_2-VASc e HAS-BLED, foi comparada a proporção de doentes que tiveram eventos com os valores teóricos correspondentes, usando o teste Binomial.

Resultados: Foram incluídos 64 doentes. Registaram-se 15 mortes, 6 eventos tromboembólicos e 7 hemorragias. Não foram encontradas diferenças significativas entre as estratégias de hipocoagulação no respeitante à sobrevida e tempo livre de hemorragia. No entanto, o tempo livre de eventos tromboembólicos é inferior no grupo dos doentes não hipocoagulados (log-rank = 0.034). Não se verificaram diferenças significativas na mortalidade e eventos tromboembólicos e hemorrágicos entre os estádios da doença renal crónica. A percentagem de eventos tromboembólicos foi inferior ao risco previsto para todos os níveis do score CHA_2DS_2-VASc. Relativamente ao score HAS-BLED, apenas na pontuação 2 e 3 a proporção de doentes com hemorragia é estatisticamente semelhante ao valor previsto para a população geral, com um número aumentado de eventos em doentes HAS-BLED 1.

Conclusões: A anticoagulação oral em doentes transplantados renais parece ser segura e eficaz. Os scores CHA_2DS_2-VASc e HAS-BLED não parecem capazes de aferir corretamente o risco tromboembólico e hemorrágicos nestes doentes.

PALAVRAS-CHAVE: transplante renal, fibrilação auricular, hipocoagulação, anticoagulantes orais diretos, antagonistas da vitamina K

ABSTRACT

Introduction: Atrial fibrillation is common among kidney transplant recipients, and it is associated with worse outcomes, as mortality and thromboembolic events. However, the efficacy and safety of vitamin K antagonists and direct oral anticoagulants in kidney transplant recipients is not yet established, and guidelines do not provide recommendations on this topic, nor the risk scores CHA_2DS_2-VASc or HAS-BLED are validated for this population. We aimed to assess the benefit/risk of oral anticoagulation in kidney transplant recipients with atrial fibrillation, and the accuracy of the scores in predicting thromboembolic and hemorrhagic events.

Subjects and Methods: Retrospective cohort study, including patients undergoing kidney transplantation from 2005 to 2020, with a diagnosis of atrial fibrillation after transplantation, without concomitant presence of prosthetic valve or stent. Demographic and clinical characteristics were assessed, as well anticoagulation strategy, thromboembolic and bleeding events, and mortality. Kaplan-Meier with log-rank test were used, comparing overall survival and time free of thromboembolic and bleeding events between anticoagulation strategies. We also compared the percentage of complications according chronic kidney disease stage using Fisher's exact test and Kaplan-Meier with log-rank test. To evaluate the performance of the CHA_2DS_2-VASc and HAS-BLED risk scores, we compared the proportion of patients that had an event with the corresponding theoretical values, through the Binomial test.

Results: 64 patients were included. We recorded 15 deaths, 6 thromboembolic events and 7 hemorrhages. No significative differences between anticoagulation strategies were found regarding survival or time free from major bleeding. However, time free from thromboembolic events is lower among the non-anticoagulated group (log-rank = 0.034). There were no significative differences on mortality, thromboembolic events or bleedings between chronic kidney disease stages. The percentage of thromboembolic events was lower than predicted risk at all levels of the CHA_2DS_2-VASc score. Concerning to HAS-BLED score, only patients scored with 2 and 3 points had a proportion of bleeding event statistically similar to the predicted value for the general population, with a higher number of events in patients scored 1 point.

Conclusions: Oral anticoagulation in kidney transplant recipients appears to be safe and is effective. The CHA_2DS_2-VASc and HAS-BLED scores do not seem to correctly assess the thromboembolic and bleeding risk in transplant patients.

KEY-WORDS: kidney transplantation, atrial fibrillation, anticoagulation, direct oral anticoagulants, vitamin K antagonists

ABBREVIATIONS LIST

AF – Atrial fibrillation

AMI – Acute myocardial infarction

CHUdSA – Centro Hospitalar Universitário de Santo António

CNI – Calcineurin inhibitors

CKD – Chronic kidney disease

DOAC – Direct oral anticoagulants

ESKD – End-stage kidney disease

KT – Kidney transplantation

KTR – Kidney transplant recipients

OAC – Oral anticoagulation

TIA – Transient ischemic attack

VKA – Vitamin K antagonists

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Figure 2 – Kaplan-Meier curves for all-cause mortality, thromboembolic events, and hemorrhagic events, during the first 120 months of follow-up, comparing the CKD stage at time of AF diagnosis: CKD 1-3 (blue) and CKD 4-5 (green). The value of the log-rank test for each outcome is presented. These results include all patients, not discriminating the anticoagulation strategy. 12

INTRODUCTION

Atrial fibrillation (AF) is an highly prevalent cardiac arrhythmia, with an important morbimortality rate [1]. Its increased prevalence in end-stage kidney disease (ESKD) patients is already well-known, 10- to 20-fold higher than in general population [2].

Kidney transplantation (KT) is the best treatment for ESKD patients, with improvements in survival and quality of life compared with dialysis [3, 4]. Although the improvement of renal function seems to affect positively the incidence and potential complications of AF, the use of immunosuppressive drugs, namely calcineurin inhibitors (CNI), and the common insulin resistance and metabolic syndrome after the surgery confer an increased cardiovascular risk and have negative role in the development of the arrhythmia and its consequences [5, 6].

In ESKD patients, the management of AF is controversial: current guidelines are inconsistent and not clear in which is the best anticoagulant strategy for those patients, nor the existing scores were validated for this population, having worse predictive value [1, 7-10]. The efficacy and safety of vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC) in kidney transplant recipients (KTR) is not yet established [5, 11].

The aim of the present study is to assess the benefit/risk of oral anticoagulation in KTR with AF, and evaluate which is the best anticoagulant to choose. As a secondary objective, we intend to evaluate the accuracy of the CHA_2DS_2-VASc and HAS-BLED risk scores in predicting thromboembolic and hemorrhagic events, respectively, in our population.

SUBJECTS AND METHODS

This was a single-centre retrospective cohort study conducted on Nephrology Service, of Centro Hospitalar Universitário de Santo António (CHUdSA), Porto, Portugal, approved by the local ethics committee (registration number 2022.236(224-DEFI/198-CE)).

A retrospective analysis was carried out of the electronic clinical files of patients undergoing kidney transplantation at CHUdSA from January 2005 to December 2020. Only adult patients (age ≥ 18 years) with a diagnosis of AF after transplantation were included, with a sampling method not random, for convenience and consecutive. Exclusion criteria were diagnosis of AF prior to transplantation, and presence of prosthetic valve or stent.

For sample characterization, the following variables were evaluated: age, gender, weight, height, anticoagulation strategy (none, DOAC or VKA), renal function parameters (creatinine, urea),

chronic kidney disease (CKD) etiology, immunosuppressive therapy, other comorbidities, namely to access CHA_2DS_2-VASc and HAS-BLED scores (heart failure/left ventricular dysfunction, arterial hypertension, diabetes mellitus, previous thromboembolic events, peripheral arterial disease, coronary disease, aortic disease, liver dysfunction, previous bleeding events or bleeding predisposition, anemia, alcohol consumption, treatment with antiplatelet or anti- non-steroidal inflammatory agents), thromboembolic events, bleeding events and mortality. The list of variables evaluated are defined in Table I.

Definition of thromboembolic and hemorrhagic events

Major thromboembolic events were defined as the occurrence of ischemic stroke, transient ischemic attack (TIA), acute myocardial infarction (AMI), pulmonary thromboembolism or renal artery infarction. Major bleeding events were defined as intracranial, gastrointestinal, genitourinary, retroperitoneal or other hemorrhage requiring transfusion or leading to the patient's death.

Statistical analysis

Statistical analysis was performed using the IBM® program – SPSS® Statistics version 27.0 for Windows. Continuous variables were reported as means and standard deviations if they followed normal distribution, or medians and minimum and maximum values when did not meet this condition. Categorical variables were expressed as frequencies and percentages.

It is defined as a 95% confidence interval, with a significance level of α=0.05. To respond to the main objective of the study, the Kaplan-Meier method with log-rank test were used, comparing overall survival and time free from thromboembolic and bleeding events during the follow-up period, between non-anticoagulated, anticoagulated with VKA and anticoagulated with DOAC patients. We also compared the percentage of complications (death, thromboembolic events or major bleedings) according CKD stage. For this analysis, Fisher's exact test and the Kaplan-Meier method with log-rank test were used.

To evaluate the performance of the CHA_2DS_2-VASc and HAS-BLED risk scores, the thrombotic and hemorrhagic risk of each patient was calculated at the time of initiation the oral anticoagulation (OAC), the proportion of patients at each level of the score that had an event at first year of

follow-up was determined, and it was compared with the corresponding theoretical values, through the Binomial test.

RESULTS

Cohort description

From January 2005 to December 2020, 1601 patients underwent kidney transplantation at our institution. Of these, 106 (6.6%) patients were diagnosed with AF, before or after transplantation, but only 64 (4%) were included in the study. The cohort had a median follow-up period of 42 months (ranging from 1 to 136 months). The mean age at the time of AF diagnosis was 61.6 years, and 42 patients (65.6%) were male. The anthropometric and clinical characteristics of the patients are illustrated in Table II.

Comparison of outcomes between anticoagulation strategies

A total 30 patients (46.9%) were treated with VKA (warfarin or acenocoumarol), 21 patients (32.8%) with apixaban, 4 patients (6.3%) with rivaroxaban and 2 patients (3.1%) with edoxaban. Seven patients (10.9%) did not undergo OAC.

Overall, 15 patients (23.4%) died, after a mean follow-up time of 62.87 ± 43.94 months, since the diagnosis of AF – 11 patients under VKA, 2 patients treated with DOAC and 2 patients with none OAC regimen. Six patients (9.4%) had thromboembolic events, and 7 patients (10.9%) had major bleeding, during the follow-up period.

There was no significative difference between VKA, DOAC or none OAC regarding survival or time free from major bleeding. However, survival free from thromboembolic events is lower among the non-anticoagulated group (log-rank = 0.034), as shown in Figure 1.

In the first 5 years of follow-up 3 thromboembolic events occurred, all after the first year, consisting in 1 renal artery infarction and 2 ischemic strokes. After this period, there were 2 ischemic strokes (at 70 and 120 months) and one AMI at 109 months. Concerning major bleedings, during the 1st year of follow-up was registered 6 events, namely 2 intracranial bleedings, 1 gastrointestinal hemorrhage, 1 hemorrhagic shock and 1 other bleeding requiring transfusion. We also found 2 another gastrointestinal bleedings, the first one in the 12th month of follow-up, and the second one at 90 months after AF diagnosis.

We also performed a comparison of the outcomes according to CKD stage: there was no significative differences on mortality, thromboembolic events or major bleedings between CKD stage 1-3 or 4-5 patients during the follow-up period, as shown in Figure 2 and Table III.

Risk scores performance in the cohort

All patients scored intermediate or high risk in CHA_2DS_2-VASc and HAS-BLED scores: concerning to stroke, 11 patients (17.2%) had intermediate risk and 53 patients (82.8%) had high risk, scoring ≥ 2 points, while regarding the bleeding risk, 39 patients (60.9%) were at moderate risk and 25 patients (39.1%) had high risk (≥ 3 points in HAS-BLED score).

In Table IV we compare the theoretical risk of stroke, TIA or systemic embolism at 1 year of OAC corresponding to each score of CHA_2DS_2-VASc with the percentage of events occurring in the 1st year of follow-up of our cohort, and in Table V the theoretical risk of bleeding events and the percentage of events that occurred in the same period in this sample according to the HAS-BLED score [12, 13]. Only at 2 and 3 points on the HAS-BLED score the proportion of patients with a bleeding event is statistically similar to the predicted value for the general population.

DISCUSSION

AF is a very common arrhythmia among patients with CKD, particularly in patients undergoing KT. In our retrospective cohort study, 6.6% of patients undergoing KT between 2005 and 2020 had AF, which is consistent with the prevalence described in 2 meta-analysis from 2018, which reported values between 4.8 and 7% [5, 14]. Thongprayoon *et al.*, in their meta-analysis also found an incidence of AF of 4.9% after kidney transplantation [5], similar to the percentage of patients included in our study (4%), although we excluded some patients with AF diagnosed after KT due to other criteria.

These data support that AF is more prevalent in KTR than in the general population, which has an estimated prevalence between 2 and 4% [1]. Several causes may explain these results, namely the fact that KTR present common risk factors for the development of AF such as arterial hypertension, diabetes mellitus and obesity, factors associated with CKD as endothelial dysfunction and changes in phospho-calcium homeostasis, and factors related to KT such as postoperative stress and the use of immunosuppressive drugs that are associated with insulin resistance and metabolic syndrome [5, 15, 16].

AF in KTR is associated with worse outcomes, namely increased mortality, allograft lost and thromboembolic events [5]. However, there are still no guidelines on the best management strategy for these patients, namely when and which anticoagulant strategy to use [1, 9]. Our study aimed to determine whether OAC is effective and safe in patients undergoing transplant. We found no significative differences between OAC strategies (VKA, DOAC or none OAC) regarding survival or time free from major bleeding, but higher rates of thromboembolic events among the non-anticoagulated group, which supports that OAC is effective in preventing thromboembolic events in transplant patients.

Our analysis did not find significative differences in outcomes between patients anticoagulated with DOAC or under VKA. Within the group of anticoagulated patients, 4 individuals had thromboembolic events, including 3 taking VKA (10% of patients under VKA) e 1 taking DOAC (3.7%), and 7 patients had major bleeding, 6 taking VKA (20%) and 1 on DOAC (3.7%), during the follow-up period. Although not statistically significant (log-rank = 0.155 in survival analysis), there is a tendency towards a lower number of hemorrhages in the group under DOAC. We found one study comparing these 2 OAC strategies in KTR, which showed no thromboembolic events during the mean follow-up of 14.1 ± 13 months, but found a lower rate of bleeding events in patients on DOAC comparing to VKA (p=0.037) [17]. Also, in the study of Bixby *et al.* with 197 KTR, there was no significative difference in the time-to-event analysis between warfarin and DOAC in major bleeding or thromboembolic events (p=0.15) [18]. Parker *et al.* evaluated 31 patients undergoing KT taking DOAC, did not find any thrombotic events and registered 4 hemorrhages (2 major and 2 minor), with a risk of hemorrhage of 6.9 per 100 patient-years at risk [19]. Another retrospective cohort study with 42 KTR recorded no thromboembolic events and 3 (7.1%) bleedings during one-year follow-up period [11]. Basic-Jukic *et al.* found that over a median follow-up of 2 years on a cohort of 23 patients under DOAC no thromboembolic events occurred and noticed 2 bleeding events (8.7%) [6].

The existing bibliography on this subject is scarce, and the current topic in focus is whether or not DOAC are safe in patients undergoing KT, because although in the general population they show several advantages over VKA, such as their pharmacokinetic and pharmacodynamic properties (short half-life, rapid onset and offset of action, absence of food interactions and few drug interactions) and the absence of the need for laboratory monitoring, it is necessary to take into account that in CKD and especially in the terminal stages, the clearance of DOAC may be compromised, as all these drugs are to some extent eliminated by the kidney, with a risk of accumulation and an increased risk of bleeding [6, 11, 19]. Furthermore, in transplant patients,

despite the limited existing data, DOAC seem to interact with calcineurin inhibitors (CNI), due to the fact that they share some metabolic pathways, such as CYP3A4 and P-glycoprotein, which may culminate in increased plasma levels of the DOAC and CNI trough concentration, requiring dose adjustment [6, 11, 19-22]. In fact, in 2015 Heidbuchel *et al.* published a recommendation for the non-use of dabigatran and CNI concomitantly (none of our patients were anticoagulated with dabigatran) [20]. Although the existing studies are scarce and the samples are small, from the results described above, DOAC appear to be safe and effective in KTR, but further controlled studies and with larger samples are needed.

We also performed an analysis comparing outcomes between CKD stages, namely CKD 1-3 versus CKD 4-5: there was no significative differences on mortality, thromboembolic events or major bleedings during the follow-up period. However, in CKD 4-5 patients there is a higher mortality rate (33.3% vs 20.0%) and a higher number of hemorrhages (16.7% vs 8.9%), but a lower number of thromboembolic events (5.6% vs 11.1%). No further analysis was performed to investigate possible confounders.

Although the CHA_2DS_2-VASc score is widely used to stratify the risk of ischemic stroke in patients with AF and the HAS-BLED score to predict the risk of bleeding, these scores are not validated for patients undergoing kidney transplantation and AF [1]. To understand whether these risk scores apply to the population of kidney transplant recipients, we aimed to assess whether the percentage of thromboembolic and hemorrhagic events that occurred in our cohort at the first year of follow-up correspond to the theoretical value for each risk level of the CHA_2DS_2-VASc and HAS-BLED scores, respectively. As would be expected, all patients were at moderate or high risk due to their renal dysfunction and associated comorbidities, such as hypertension. In our analysis, as no thromboembolic events occurred in the 1st year, the percentage of events was lower than predicted risk at all levels of the CHA_2DS_2-VASc score. Concerning to HAS-BLED score, we found that only at 2 and 3 points on the score the proportion of patients with a bleeding event is statistically similar to the predicted value for the general population, with a higher number of events in patients scored 1 (7.7% in our cohort versus the theoretical 3.4% risk). It is remarkable to note that, despite not statistically significant, even in individuals scored 3, the percentage of bleedings were higher (11.8% versus 5.8%).

In a recent study, Hau et al. evaluated the incidence of bleeding in 204 patients underwent KT and the predictive value of the HAS-BLED score, and they found a moderate predictive accuracy for postoperative hemorrhages (AUC 0.72) [23]. Furthermore, from HAS-BLED > 3, this score seems to be an independent predictor of postoperative hemorrhages in patients undergoing KT [23].

However, this is the only study we found that investigates the validity in kidney transplant patients of the most commonly used risk scores in AF. It is important to note that KTR have unique risk factors that contribute to changes in the hemostatic system, with paradoxically pro- and anticoagulant effects, such as CKD itself, which leads to anemia, uremia and uremic platelet dysfunction, or associated with transplantation, such as the use of immunosuppressive agents that may predispose to thrombotic microangiopathy and endothelial injury, and which, as seen, may interact with DOAC, leading to increased concentration and greater bleeding risk [24, 25].

This study has several limitations. First, it is a single-centre retrospective cohort study, without randomization, which leads to multiple biases and confounders, such as the possible underreporting of complications. Moreover, this is a study with a small number of patients, in which, despite the median follow-up time being reasonable, a limited number of events occurred, not allowing sub-analyses such as the comparison of outcomes between the different DOAC. Regarding VKA, it was not possible to assess the time in therapeutic range, so it is not possible to guarantee that all patients treated with VKA were at appropriate therapeutic levels.

Aside from the long median follow-up period, another strength of this study is the inclusion of patients in the various stages of kidney disease. To our knowledge, this is the first study conducted in Portugal to evaluate the efficacy and safety of anticoagulation strategies in KTR with AF and the validity of risk scores.

CONCLUSIONS

The use of oral anticoagulants in KTR appears to be safe and is effective in preventing thromboembolic events. Although our results are limited, it seems that the CHA_2DS_2-VASc and HAS-BLED scores do not correctly assess the thromboembolic and bleeding risk in transplant patients. Further large-scale studies and clinical trials of anticoagulation in kidney transplant recipients with AF are needed, as well as investigating the validity of existing risk scores or creating new scores focused on patients with CKD or kidney transplant.

APPENDIX

Table I – Definition of variables

Gender (female / male)
Age (in years, at the time of AF diagnosis)
Anticoagulation strategy (no – without oral anticoagulation / VKA (warfarin or acenocoumarol) / DOAC (apixaban, rivaroxaban, dabigatran or edoxaban); in case of change in therapeutic strategy, it was considered the strategy with longer duration or the one adopted at the time the thromboembolic/bleeding event occurred)
Weight (in kilograms, at the time of AF diagnosis) **Height** (in meters, at the time of AF diagnosis) **- BMI** (in kg/m^2, at the time of AF diagnosis)
Immunosuppression (immunosuppressive strategy, at the time of AF diagnosis)
Chronic kidney disease (CKD): **- CKD stage** (at the time of AF diagnosis) - **Glomerular filtration rate (GFR)** (in mL/min, at the time of AF diagnosis, using CKD-EPI Creatitine Equation method (2021)) **- Urea** (in mg/dL, at the time of AF diagnosis) **- Etiology** (of CKD)
Comorbidities: **- Congestive heart failure** (yes – clinical heart failure, moderate to severe left ventricle dysfunction, hypertrophic cardiomyopathy / no) **- Arterial hypertension** (yes / no; for HAS-BLED score, considered if systolic pressure >160 mmHg) **- Diabetes mellitus** (yes – non insulin-treated or insulin-treated / no) **- Previous thromboembolic events/stroke** (yes – stroke, transient ischemic attack or thromboembolism / no; for HAS-BLED score, yes if prior ischemic or hemorrhagic stroke) **- Peripheral artery disease** (yes / no) **- Coronary disease** (yes – prior myocardial infarction or documented coronary disease / no) **- Liver disease** (yes – cirrhosis or bilirubin >2x normal with AST/ALT/AP >3x normal / no) **- Prior major bleeding** (yes – intracranial, gastrointestinal, genitourinary or retroperitoneal hemorrhage or requiring transfusion / no) **- Anemia** (yes / no) **- Medication usage predisposing to bleeding** (yes – aspirin, clopidogrel, non-steroidal anti-inflammatory drugs / no) **- Excessive alcohol use** (yes / no)

AF – atrial fibrillation, VKA – vitamin K antagonists, DOAC – direct oral anticoagulants, BMI – body mass index, CKD – chronic kidney disease, GFR – glomerular filtration rate, AST – aspartate aminotransferase, ALT – alanine aminotransferase, AP – alkaline phosphatase, NSAID – non-steroidal anti-inflammatory drugs.

Table II – Baseline characteristics of the patients, at the time of AF diagnosis (n=64)

Age (years), mean ± SD	61.64 ± 10.053
Male, N (%)	42 (65.6)
Weight (kg), mean ± SD	72.55 ± 13.769
Height (m), mean ± SD	1.66 ± 0.101
BMI (kg/m^2), median (min-max)	24.31 (19.38-39.30)
Cause of ESKD	
- Unknown, N (%)	25 (39.0)
- IgA nephropathy, N (%)	5 (7.8)
- Autosomal dominant polycystic kidney disease, N (%)	4 (6.3)
- Focal segmental glomerulosclerosis, n (%)	2 (3.1)
- Mesangioproliferative glomerulonephritis, N (%)	3 (4.7)
- Diabetic nephropathy, N (%)	3 (4.7)
- Chronic glomerulonephritis, N (%)	9 (14.1)
- Chronic pyelonephritis, N (%)	2 (3.1)
- Chronic interstitial nephritis, N (%)	2 (3.1)
- Other, N (%)	9 (14.1)
CKD stage	
- Stage 1, N (%)	4 (6.3)
- Stage 2, N (%)	21 (32.8)
- Stage 3, N (%)	20 (31.3)
- Stage 4, N (%)	12 (18.8)
- Stage 5, N (%)	6 (9.4)
GFR (mL/min), mean ± SD	49.51 ± 25.411
Urea (mg/dL), median (min-max)	67.50 (20.00-299.00)
Immunosuppression regimen (in addition to corticosteroid therapy)	
- None, N (%)	2 (3.1)
- Tacrolimus, N (%)	7 (10.9)
- Mycophenolate mofetil, N (%)	1 (1.6)
- Tacrolimus + Mycophenolate mofetil, N (%)	48 (75.0)
- Mycophenolate mofetil + Cyclosporin, N (%)	5 (7.8)
- Mycophenolate mofetil + Sirolimus, N (%)	1 (1.6)
Comorbidities:	
- Congestive heart failure, N (%)	23 (35.9)
- Arterial hypertension, N (%)	63 (98.4)
- Diabetes mellitus, N (%)	25 (39.1)
- Insulin-treated, N (%)	11 (17.2)

- Non insulin-treated, N (%)	14 (21.9)
- Previous thromboembolic events/stroke, N (%)	10 (15.6)
- Peripheral artery disease, N (%)	8 (12.5)
- Aortic plaque, N (%)	2 (3.1)
- Coronary disease, N (%)	8 (12.5)
- Liver disease, N (%)	1 (1.6)
- Prior major bleeding, N (%)	6 (9.4)
- Anemia, N (%)	25 (39.1)
- Medication usage predisposing to bleeding, N (%)	18 (28.1)
- Excessive alcohol use, N (%)	6 (9.4)
CHA_2DS_2-VASc score	
- Low risk (0 points), N (%)	0 (0)
- Intermediate risk (1 point), N (%)	11 (17.2)
- High risk (≥ 2 points), N (%)	53 (82.8)
HAS-BLED score	
- Low risk (0 points), N (%)	0 (0)
- Moderate risk (1-2 points), N (%)	39 (60.9)
- High risk (≥ 3 points), N (%)	25 (39.1)

SD – standard deviation, BMI – body mass index, IgA - immunoglobulin A, CKD – chronic kidney disease, GFR – glomerular filtration rate.

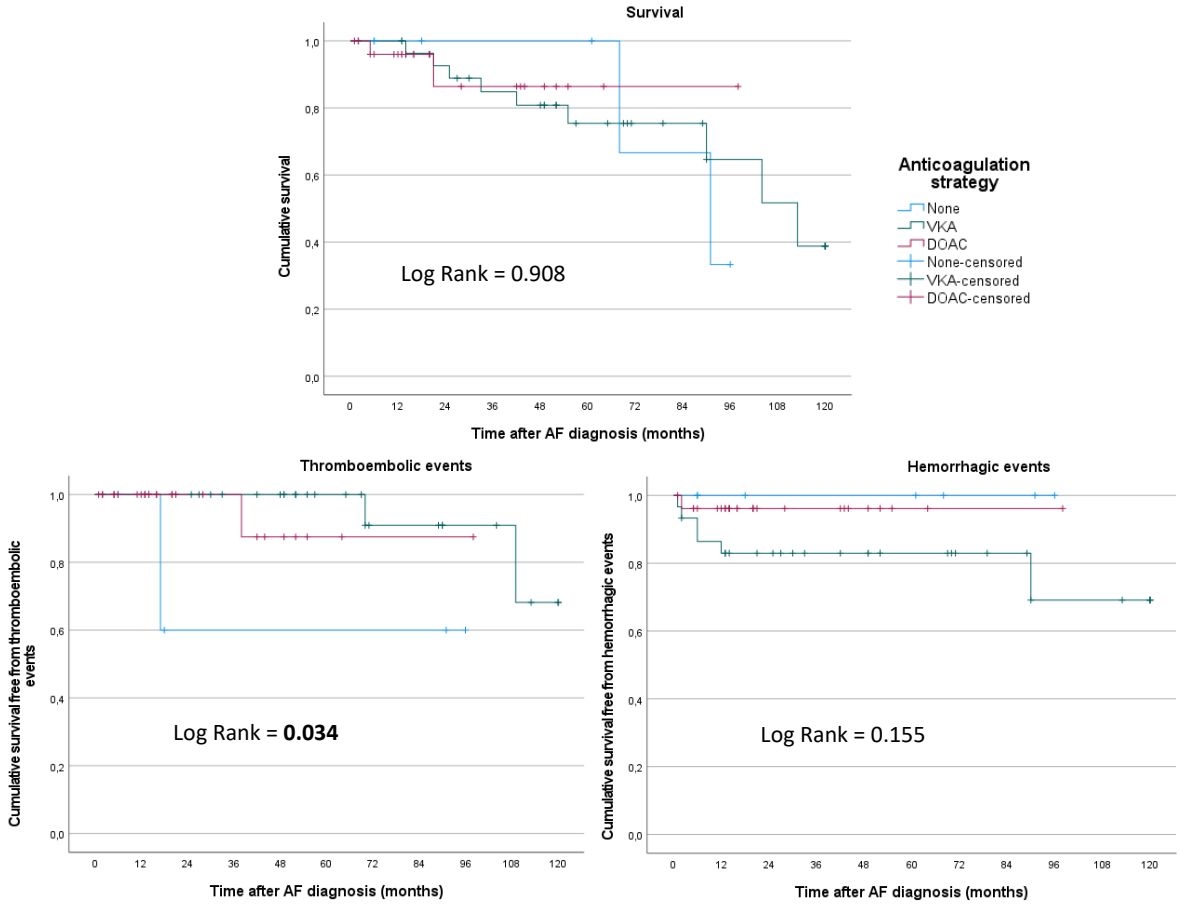

Figure 1 – Kaplan-Meier curves for all-cause mortality, thromboembolic events, and hemorrhagic events, during the first 120 months of follow-up, comparing VKA (green), DOAC (red) and none OAC (blue). The value of the log-rank test for each outcome is presented.

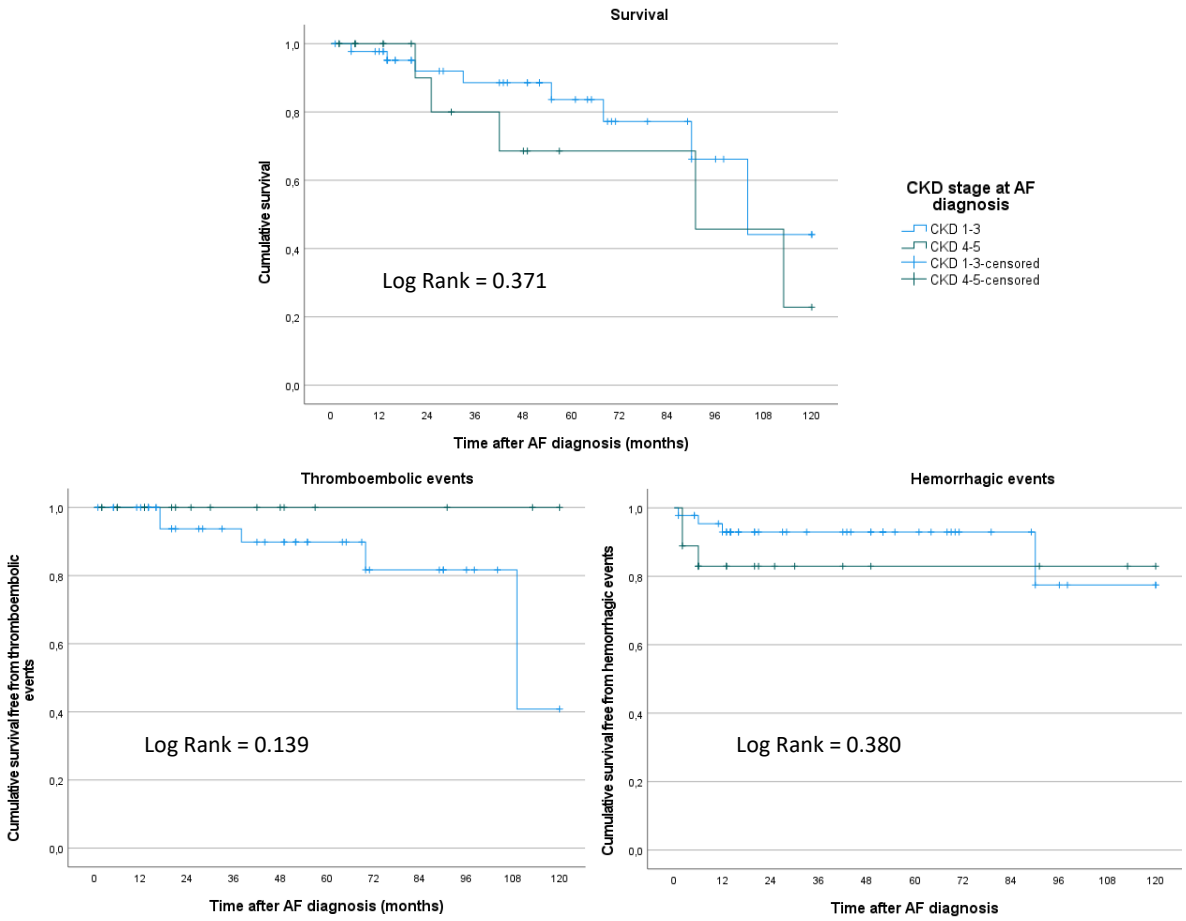

Figure 2 – Kaplan-Meier curves for all-cause mortality, thromboembolic events, and hemorrhagic events, during the first 120 months of follow-up, comparing the CKD stage at time of AF diagnosis: CKD 1-3 (blue) and CKD 4-5 (green). The value of the log-rank test for each outcome is presented. These results include all patients, not discriminating the anticoagulation strategy.

Table III – Comparison of outcomes according to CKD stage and anticoagulation strategy.

	CKD stage 1-3	**CKD stage 4-5**	**p-value**
Mortality	9/45 (20.0%)	6/18 (33.3%)	
- Patients with no OAC (N= 6)	1/3 (33.3%)	1/3 (33.3%)	1.000
- Patients on VKA (N=30)	6/18 (33.3%)	5/12 (41.7%)	0.712
- Patients on DOAC (N=27)	2/24 (8.3%)	0/3 (0%)	1.000
Thromboembolism	5/45 (11.1%)	1/18 (5.6%)	
- Patients with no OAC (N= 6)	2/3 (66.7%)	0/3 (0%)	0.400
- Patients on VKA (N=30)	2/18 (11.1%)	1/12 (8.3%)	1.000
- Patients on DOAC (N=27)	1/24 (4.2%)	0/3 (0%)	1.000
Bleeding	4/45 (8.9%)	3/18 (16.7%)	
- Patients with no OAC (N= 6)	0/3 (0%)	0/3 (0%)	-
- Patients on VKA (N=30)	4/18 (22.2%)	2/12 (16.7%)	1.000
- Patients on DOAC (N=27)	0/24 (0%)	1/3 (33.3%)	0.111

CKD – Chronic kidney disease, OAC – oral anticoagulation, VKA – vitamin K antagonists, DOAC – direct oral anticoagulants.

Table IV – Application of the CHA_2DS_2-VASc risk score to the cohort [12]

Score	Theoretical risk of stroke, TIA or systemic embolism at 1 year of follow-up	Number of patients with particular score in the cohort	Thromboembolic events (%)	P-value
1	0.9%	10	0	**<0.001**
2	2.9%	16	0	**<0.001**
3	4.6%	10	0	**<0.001**
4	6.7%	10	0	**<0.001**
5	10.0%	7	0	**<0.001**
6	13.6%	1	0	-
8	15.2%	1	0	-

Table V – Application of the HAS-BLED risk score to the cohort [13]

Score	Theoretical risk of bleeding events at 1 year of follow-up	Number of patients with particular score in the cohort	Major bleeding events (%)	P-value
1	3.4	13	7.7	**0.034**
2	4.1	22	4.5	0.602
3	5.8	17	11.8	0.058
4	8.9	3	0	**<0.001**
5	9.1	1	0	-

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