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Full Length Article

Differences between patient-driven adherence to vitamin K antagonists and direct oral anticoagulants. Do few missed doses matter? ACO-MEMS Study

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ABSTRACT

Introduction: Lack of INR controls might affect the adherence to direct oral anticoagulants (DOAC). The vast majority of studies that addresses adherence to anticoagulants are retrospective and based on pharmacy refill data. Our aim was to compare the adherence between vitamin K antagonists (VKA) and DOAC and to analyze the clinical relevance of non-adherence.

Materials and methods: A prospective two-arm observational cohort study was performed in two Spanish public hospitals. Adherence was assessed by Medication Event Monitoring System. Relationship between adherence and events during follow-up and time in therapeutic range (TTR) in the VKA group were analyzed.

Results: 257 patients were included (132 DOAC and 125 VKA). Monitoring time was 120 days (101 − 133). Patients in VKA group showed higher taking adherence (97.9% vs. 95.8%) and less non-adherent patients of > 5% and > 10% of the doses, without differences in > 20% of the doses. Taking adherence was strongly associated with TTR (AUC: 0.89, CI 95%: 0.81–0.97 of TTR for detection of non-adherent patients of > 10% of doses). During a follow-up of 1.8 years (1.6–2) non-adherent patients of > 5% of doses presented more thromboembolic events (HR 6.1, CI95% 1.3–28.1).

Conclusions: Although adherence to oral anticoagulant therapy was excellent, it was higher to VKA than to DOAC. Time in therapeutic range was highly sensitive to few missed doses of AVK. Non-adherence of > 5% of prescribed doses had high clinical relevance.

1. Introduction

Atrial fibrillation (AF) is currently one of the most important public health problems because of its socio-health and economic impact. Oral anticoagulation with vitamin K antagonists (VKA) had been for ages the cornerstone of the treatment in AF patients. However, the main concern with VKA is the narrow therapeutic range and the need for regular checks of the international normalized ratio (INR) in order to adjust the dose. Despite all the efforts, the proportion of patients out of the ideal therapeutic range of the INR (TTR) is still between 32 and 47% [1,2]. In this setting, direct oral anticoagulants (DOAC) proved to have a superior efficacy with a better safety profile [3], emerging as the perfect drug. Predictable and stable pharmacokinetics that avoids the need of frequent controls is their greatest strength, but this theoretical advantage could translate into a lack of adherence that could diminish effectiveness in real life, with potentially serious consequences. Moreover, non-adherence is rarely taken into account in clinical trials, and could play a significant role in the perceived efficacy of a drug [4]. In the context of poor INR controls, patient driven non-adherence to VKA is usually under-recognized and studied [5]. The problem could be

Abbreviations: AF, atrial fibrillation; INR, international normalized ratio; VKA, vitamin K antagonists; DOAC, direct oral anticoagulants; MEMS, Medication Event Monitoring System; TTR, time in therapeutic rang; ACEI, angiotensin converting enzyme inhibitor; ARA, angiotensin II receptor antagonist; ASA, acetylsalicylic acid; LVEF, left ventricular ejection fraction; OAD, once daily regimen; BID, twice daily regimen; IQR, interquartile range; ROC, receiver operating characteristic curve; AUC, area under the curve; ACS, acute coronary syndrome; GI, gastrointestinal; PDC, proportion of days covered

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worse with DOAC, since the lack of reinforcement that frequent blood controls provide could be related to even a worse adherence. In addition, taking into account that one of the main indications for DOAC prescription is poor anticoagulation control [6], we could be wrongly pre-selecting non-adherent patients to DOAC treatment. Studying real life adherence becomes a priority due to the increasing number of patients receiving DOAC.

The majority of clinical trials have considered the threshold of > 20% of missed doses to classify a patient as non-adherent [7–12]. The clinical relevance of lower levels of non-adherence to oral anticoagulants is unknown.

The primary objective of this study was to compare the adherence between VKA and DOAC using an electronic medication control device (MEMS). The relationship between adherence and clinical outcomes and the impact of adherence on INR control in patients receiving VKA were also evaluated.

2. Material and methods

2.1. Study design and population

The study was a prospective, two-arm observational cohort study. One study arm consisted of patients receiving DOAC and the other consisted of patients under VKA, who underwent regular INR measurements in their reference centers. Adherence to the treatment was measured using the electronic Medication Event Monitoring System (MEMS, WestRock, Switzerland). The patients were recruited in the outpatient cardiology clinic of two Spanish public hospitals. All patients diagnosed of non-valvular AF under chronic anticoagulant treatment (Acenocoumarol, Rivaroxaban, Dabigatran or Apixaban) were considered eligible. Patients had to be already under anticoagulation treatment at the time of enrolment. All patients provided written informed consent. The exclusion criteria were: poor short-term vital prognosis, valvular prostheses, severe valve disease, cognitive impairment and patients who used a weekly pillbox.

Patients were provided with complete information about the aims of the study, including the measure of anticoagulation adherence, but were not informed about the exact mechanism of MEMS to avoid bias in the results. The study conformed to the principles of the Helsinki Declaration and was approved by the local Ethics Committee of Clinical Research.

2.2. Adherence measurement

The caps of the MEMS containers recorded exact date and time of every opening. Non-opening of the container was considered as *missed dose.* Opening not more than two hours from the prescribed time was considered as *on-schedule dose*, and opening in any other moment was considered as *mistimed dose*.

Taking non-adherence was calculated according to the following formula: number of missed doses/number of prescribed doses x100. *Taking adherence* (i.e. doses actually taken, including both on-schedule doses and mistimed doses) was defined as 100 – taking non-adherence. *Schedule adherence* (i.e. doses taken on schedule) was calculated as follows: number of on-schedule doses / number of prescribed doses x 100. Temporary discontinuation for medical reasons and no treatment planned days in VKA patients were excluded from the analysis.

Different non-adherence thresholds were evaluated in order to codify the patient as non-adherent (i.e. 20%-non-adherent, 10%-non-adherent and 5%-non-adherent if taking non-adherence was > 20%, 10% and 5%, respectively, of total prescribed doses).

2.3. Sample size

Calculation of the sample size was made assuming the threshold of 20% of the doses missed to define a patient as being non-adherent as generally accepted in the literature [7–12]. For VKA patients non-adherence was estimated to be around 35% according to the scarce previously published data using MEMS [8]. To detect a difference in non-adherence of 15% between groups and assuming an alpha error of 0.05 and power of 80%, 137 patients for each study group were needed. Considering a potential loss during follow up of 10%, sample size was estimated in 152 patients for each group.

2.4. Study protocol

In the first visit eligibility was confirmed, informed consent signed, and a questionnaire was filled. This questionnaire, with an estimated time of completion of 30 min, included questions on sociodemographic variables, knowledge on AF, degree of motivation for health behaviours, tests on Health Literacy, as well as various psychological tests.

Two weeks later, an activated MEMS was given to every patient containing medication for 3 months. All the patients were instructed to take medication only from the container and not to open it for other reasons. None of them knew that the device contained a microchip that registered every opening of the container. Patients on VKA had their regular INR controls in their reference centers. All of them were asked to discard the remaining pill if the prescribed dose was not a whole tablet, so that the opening of the device corresponded to the daily dose. At the 3 months follow-up visit the containers were refilled and any temporary treatment discontinuation for medical reason was reviewed. A last follow up visit was scheduled at 6 months, when once again any treatment discontinuation was checked, the MEMS was returned back, and the adherence data were transferred to a computer and reviewed using the medAmigo Software.

2.5. Duration and follow-up

The inclusion period of the study was from April 2015 to June 2016. Adherence was monitored for a mean of 120 days (interquartile range (IQR): 101–133). Ischemic and hemorrhagic events were followed until June 2017 (mean follow-up 1.8 years). TTR of patients receiving VKA was measured up to 12 months after their inclusion using the Rosendaal method [13].

2.6. Definitions

Permanent discontinuation of oral anticoagulation was defined as definitive suspension of the treatment, and temporary discontinuation if transitory interruption due to a medical incident and/or indicated by a physician happened. Poor control of INR was considered when TTR was lower than 65% within a year after the inclusion in the study [14]. Additional definitions are described in the Supplementary material online.

2.7. Statistical analysis

Filemaker database was used to collect data and SPSS program version 19.0 for Mac OS for statistical analysis (SPSS Inc., Chicago, Illinois, USA). Quantitative variables are presented as mean ± standard deviation, or median and IQR. Normally distributed, continuous variables were evaluated using the Student *t*-test and for those not normally distributed Mann-Whitney *U* test was used.

Qualitative variables were expressed as number of cases and percentage. Differences in categorical variables were evaluated with Chi-square test or Fisher's exact test if the expected value in any cell was < 5. Correlation between quantitative variables was analyzed by Pearson's, using the non-parametric ρ of Spearman for non-parametric not normally distributed.

Receiver operating characteristic (ROC) curve was applied to evaluate the discriminative ability of TTR to detect non-adherence > 10%. The area under the curve (AUC) with its corresponding 95% confidence

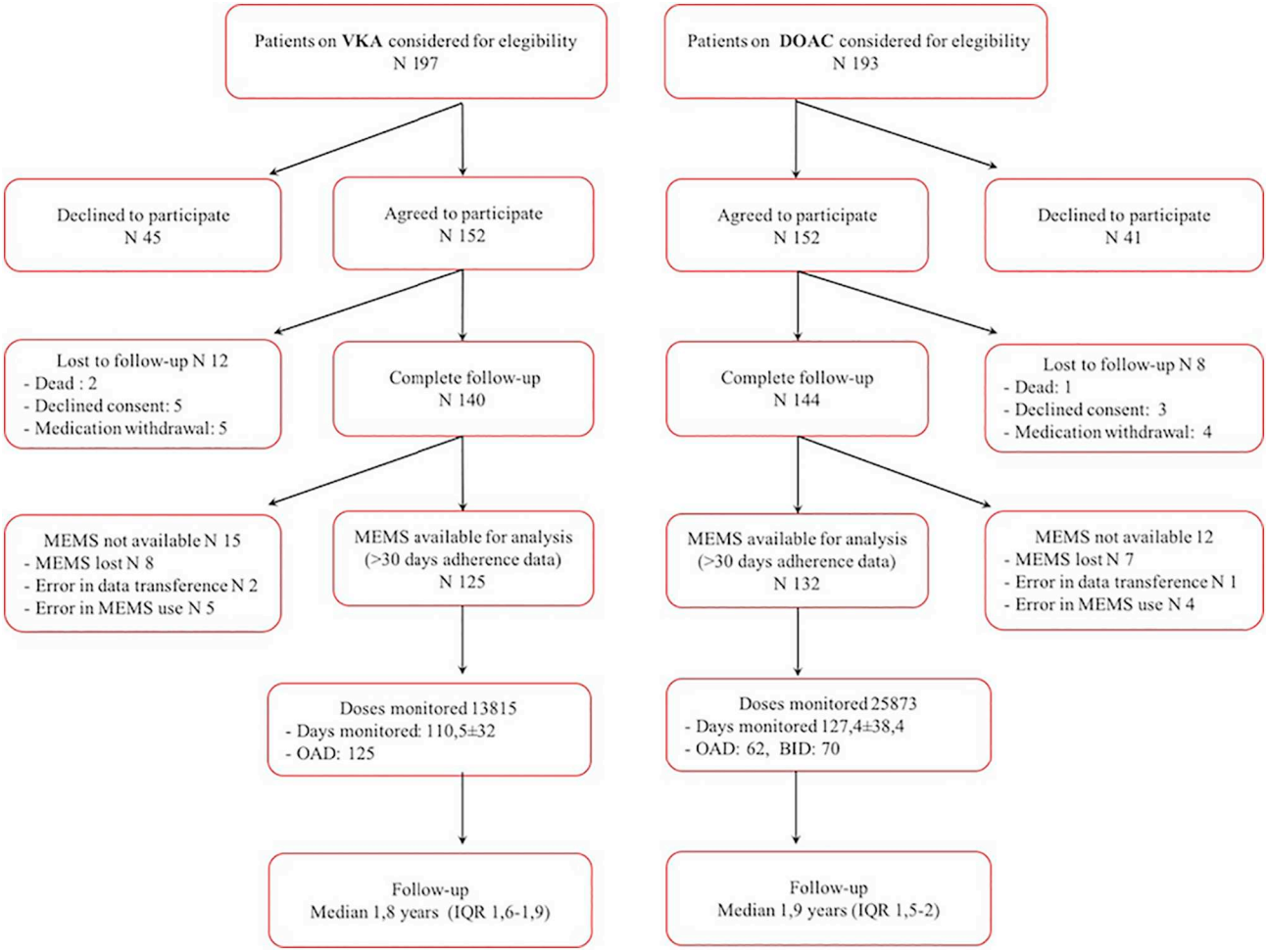

Fig. 1. Patient selection flowchart.
VKA, vitamin K antagonists; DOAC, direct oral anticoagulants; MEMS, electronic medication control device; OAD, once daily regimen; BID, twice daily regimen.

interval was calculated, and also the TTR cutoff with the most optimal values of sensitivity and specificity.

Free survival of thromboembolic events was analyzed using the Kaplan-Meier method, using the Log Rank test for comparison between patients who missed > 5% of the doses and those who missed less. A statistically significant result was considered when the value of p was < 0.05.

3. Results

The flow chart of the study is shown in Fig. 1. From out of 390 patients initially screened, 304 patients agreed to participate and were included in the study, 152 in each group. There were 47 patients in whom the MEMS could not be analyzed (27 in the VKA group and 20 in the DOAC group). Finally 257 patients were analyzed (125 VKA and 132 DOAC). Baseline characteristics of both groups are shown in Table 1.

The reasons for loss to follow-up were as follows: Three patients died during the monitoring period, eight revoked the consent, nine permanently interrupted treatment during the first month of monitoring (five in the VKA group: four due to change to DOAC and one due to bleeding, and four in the DOAC group: two were changed to VKA and two changed to another DOAC). 15 patients lost their MEMS, in three failed the reading system and nine were withdrawn for analysis because of misuse of the device (five in the VKA group and four in DOAC). Baseline characteristics of patients not analyzed ($n = 47$) didn't differed significantly from those analyzed ($n = 257$). (see analysis in Supplementary material online). INR control of VKA patients not analyzed ($n = 15$) was similar to those who were analyzed ($n = 125$) (71.9 ± 15.7 vs. 71.8 ± 15.3, $p = .98$).

3.1. Comparison of adherence

Adherence was very high both to VKA and DOAC. The proportion of 20%-non-adherent patients was very low, and there was no difference between the groups. Nevertheless, VKA group patients showed a better taking adherence and schedule adherence (Fig. 2), with a lower percentage of 5% and 10% non-adherent patients. (Fig. 3). Within DOAC group, there were no differences in the taking adherence and schedule adherence between the patients who took one daily dose versus two doses (Fig. 2). There were also no differences in the percentage of 5%, 10% or 20% non-adherent patients.

Patients in VKA group were longer under anticoagulation treatment (4.8 ± 5 Vs 1.8 ± 1.6 years, $p < .001$). Nevertheless, this variable was not associated with adherence and was not a confounding factors in the comparison between both groups (see data in the Supplementary material online).

3.2. Adherence relationship with INR control

Non-adherence was strongly associated to INR control in the VKA group. The taking adherence correlated with TTR during follow-up (R 0.42, $p < .001$). TTR showed an excellent discriminative capacity to detect 10% non-adherent patients (AUC: 0.89, 95% CI: 0.81–0.97,

Table 1
Baseline characteristics in the studied population and differences between VKA and DOAC groups. Results are shown as average ± standard deviation or n/N (%).

	VKA (N = 125)	DOAC (N = 132)	Sig (p)
Age (years)	71.7 ± 8.3	74.3 ± 6.5	0.006
Sex (female)	36.8 (46/125)	38.6 (51/132)	0.76
Body mass index (kg/m2)	29.2 ± 6.9	29.3 ± 17.2	0.98
AF and risk scores			
Anticoagulation time (years)	4.8 ± 5	1.8 ± 1.6	< 0.001
Permanent atrial fibrillation	63.2 (79/125)	46.2 (61/132)	0.005
CHADS2	1.8 ± 1.1	1.9 ± 1.3	0.37
CHA2DS2-VASC	3.3 ± 1.2	3.4 ± 1.5	0.53
HASBLED	1.6 ± 0.9	2.1 ± 1.1	< 0.001
SAMe-TT2R2	1.7 ± 1.2	1.7 ± 1.1	0.82
SAMe-TT2R2 > 2 points	28.5 (35/123)	24.2 (32/132)	0.44
Cardiovascular risk factors			
Hypertension	72.8 (91/125)	75.8 (100/132)	0.59
Dislipemia	60.8 (76/125)	56.8 (75/132)	0.52
Diabetes	22.4 (28/125)	23.5 (31/132)	0.84
Active smoking	5.6 (7/125)	9.8 (13/132)	0.20
Alcohol > 40 g/day	6.4 (8/125)	6.1 (8/132)	0.91
Cardiovascular Background			
Acute myocardial infarction	16.8 (21/125)	11.4 (15/132)	0.21
Percutaneous coronary intervention	14.4 (18/125)	10.6 (14/132)	0.36
Coronary artery bypass surgery	3.2 (4/125)	5.3 (7/132)	0.41
Heart failure	25.6 (32/125)	9.1 (12/132)	< 0.001
Ischemic stroke	8.8 (11/125)	11.4 (15/132)	0.50
Transient ischemic attack	1.6 (2/125)	4.5 (6/132)	0.17
Hemorrhagic stroke	1.6 (2 /125)	4.5 (6/132)	0.17
Peripheral embolism	1.6 (2/125)	1.5 (2/132)	0.95
Pulmonary embolism	0.8 (1/125)	0.8 (1/132)	0.97
Peripheral artery disease	13.6 (17/125)	7.6 (10/132)	0.12
Comorbidities			
Major bleeding or anemia history	14.4 (18/125)	22 (29/132)	0.11
Chronic obstructive pulmonary disease	9.6 (12/125)	18.2 (24/132)	0.048
Severe chronic kidney disease (Cr > 2)	4 (5/125)	2.3 (3/132)	0.43
Charlson comorbidity index	1.7 ± 1.7	1.7 ± 1.9	0.94
Chronic treatment			
Number of tablets per day	7.3 ± 3.8	8.1 ± 4.1	0.12
ASA	4.8 (6/125)	5.3 (7/132)	0.85
Tienopiridin	5.6 (7/125)	1.5 (2/132)	0.09
Antiarrhythmic	17.6 (22/125)	18.9 (25/132)	0.78
Digoxin	17.6 (22/125)	8.3 (11/132)	0.03
Betablocker	61.6 (77/125)	53 (70/132)	0.17
Verapamil/Diltiazem	10.4 (13/125)	9.8 (13/132)	0.88
ACEI/ARA	60.8 (76/125)	65.2 (86/132)	0.47
Statin	55.2 (69/125)	54.5 (72/132)	0.92
NSAID	8 (10/125)	8.3 (11/132)	0.92
Blood test results			
Hemoglobin (gr/dL)	14.3 ± 1.9	14.1 ± 1.3	0.25
Creatinin (mg/dL)	0.94 ± 0.23	0.95 ± 0.25	0.64
Cholesterol (mg/dL)	185 ± 48	188 ± 37	0.49
Glucose (mg/dL)	110 ± 23	107 ± 20	0.26
HbA1c (%)	6.1 ± 0.9	6.1 ± 0.7	0.96
Sociodemographic data			
Lives alone	15.2 (19/125)	22 (29/132)	0.23
Medication given by another person	6.4 (8/125)	4.5 (6/132)	0.51
Academic background			0.15
Not writing/reading	1.6 (2 /125)	0 (0 /132)	
Not full-time school	24 (30/125)	27.3 (36/132)	
High school (first years)	27.2 (34/125)	27.3 (36/132)	
High school (last years)	17.6 (22/125)	14.4 (19/132)	
Technician	20 (25/125)	12.9 (17/132)	
College	9.6 (12/125)	18.2 (24/132)	
Dificultty in understanding medical information			0.38
None/Rarely	87.2 (109/125)	83.3 (110/132)	
Sometimes/Frequently/ Always	12.8 (16/125)	16.7 (22/132)	
AF knowledge test result (0–3)	1.36 ± 0.8	1.32 ± 0.9	0.66
Health concern/motivation			0.74
Knows PA, Cholesterol, Glucose values	11.2 (14/125)	10.6 (14/132)	
Knows two values	20.8 (26/125)	26.5 (35/132)	
Knows one value	38.8 (48/125)	34.1 (45/132)	
Doesn't know any	29.6 (37/125)	28.8 (38/132)	

ACEI: Angiotensin converting enzyme inhibitor; AF: Atrial fibrilation; ARA: Angiotensin II receptor antagonist; ASA: acetylsalicylic acid.

p = .001). The cutoff of 63% of TTR showed a sensitivity of 100% and a specificity of 80% to detect non-adherence > 10%.

Fig. 4 shows TTR according to different levels of non-adherence (panel A), and the percentage of poorly controlled patients according to different levels of non-adherence (panel B). 100% of the patients who failed > 10% of the intakes were poorly controlled, compared to 27.6% of those who missed < 10%.

3.3. Events during follow-up

The median follow-up was 1.8 years (IQR: 1.6–2), without differences between both groups (mean 1.74 ± 0.25 VKA vs. 1.7 ± 0.45 DOAC, p = .40). 93.8% completed one year of follow-up, and 77.8% completed a year and a half.

There were no differences in thromboembolic or hemorrhagic events between VKA and DOAC groups during the follow-up (Table 2). Patients who failed > 5% of the doses had more thromboembolic events compared to those who failed only between 0 and 5% (HR: 6.1, 95% CI: 1.3–28.1), without differences in hemorrhagic events (see Supplementary material online). Fig. 5 shows the comparison of thromboembolic event-free survival between the two groups.

4. Discussion

To our knowledge, this is the first study that directly compares the adherence between VKA and DOAC with the MEMS system. The main findings are 1) Adherence to both anticoagulant drugs is very high, with few patients that failed > 20% of the intakes without differences between both drugs. 2) Patients taking VKA have a better adherence than DOAC patients, both in terms of taking and schedule adherence and had lower rates of 5% and 10% non-adherence. 3) TTR of patients under treatment with VKA is very sensitive to missed doses. 4) Patients who miss > 5% of the doses have more thromboembolic events in the follow-up.

The adherence to anticoagulant drugs described in the literature diverges markedly, and depends mainly on the method and definition used to measure it [15]. The vast majority of studies are retrospective, based on pharmacy refill data and estimated by the proportion of days covered (PDC). Adherence with these methods and defined as percentage of > 80% of days covered, ranges from 50%–70% to VKA [16,17] and 50–99% to DOACs [9–11]. There are several limitations with those methods, since the dispensing of the drug is not equivalent to taking it, and in most cases temporary discontinuations of the drug due to medical reasons are not taken into account and assimilated to patient-driven non-adherence. Moreover, in the case of VKAs the variability of the dose makes very difficult to calculate a reliable PDC [12].

The ability to store information regarding opening time and date in the electronic monitor as with the MEMS devices has proven to be one of the most accurate methods to measure adherence [18]. A possible limitation of this method is that patient's adherence might be influenced by knowing they are being controlled (Hawthorne Effect). Therefore any comment about the recording system of the device was avoided in our study. This could be the main reason why the percentage of patients that couldn't be analyzed in our study (15%) is slightly higher than

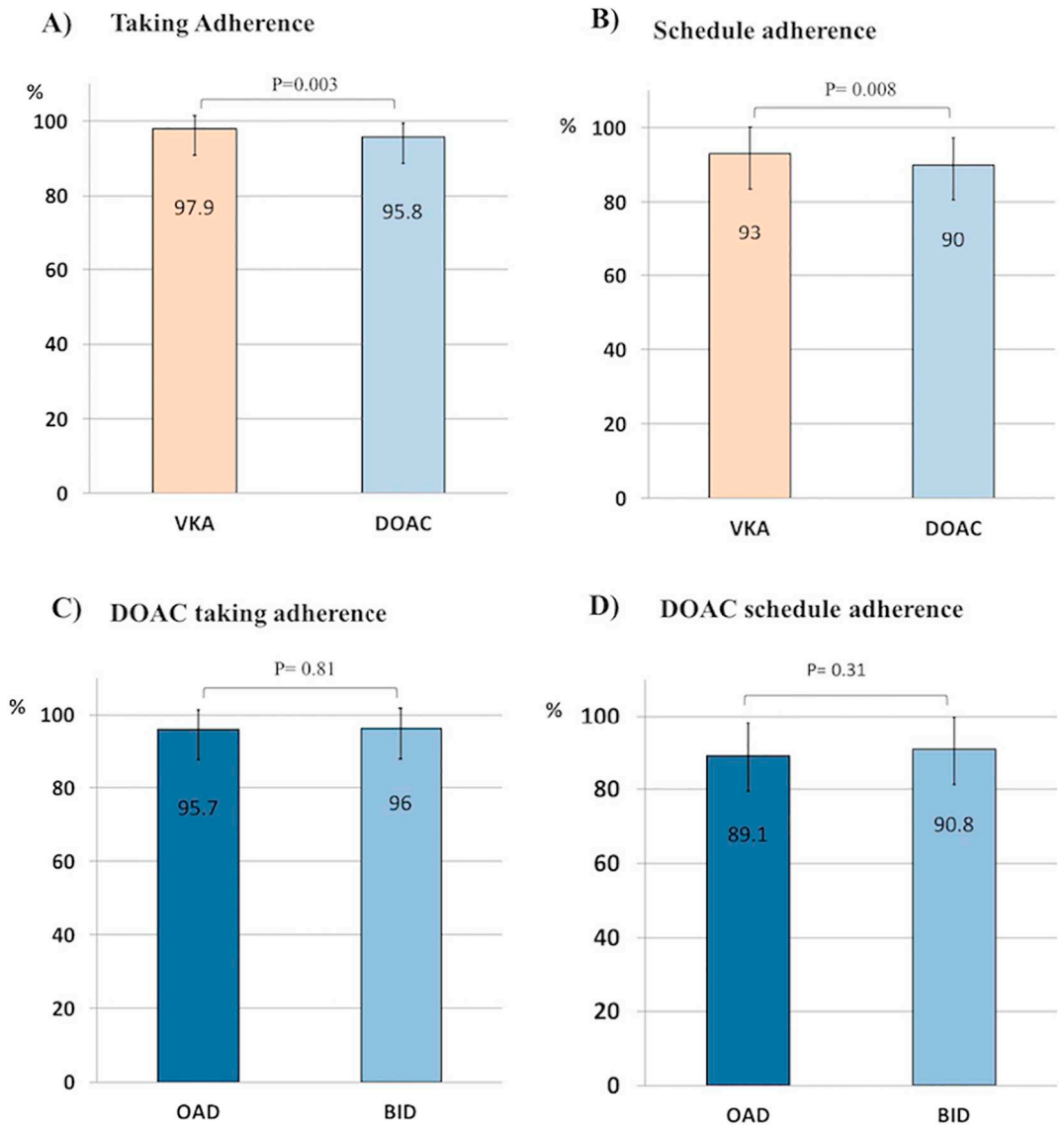

Fig. 2. Comparison of Taking adherence (panel A) and Schedule adherence (panel B) between VKA and DOAC, and Taking adherence (panel C) and Schedule adherence (panel D) between once daily vs twice daily DOAC.
Bars represent mean and standard deviation.
VKA, vitamin K antagonists; DOAC, direct oral anticoagulants; MEMS, electronic medication control device; OAD, once daily regimen; BID, twice daily regimen.

initially expected (10%) because the loss or misuse of the devise were the main causes of loss to follow-up. Indeed, this percentage is similar to other studies with MEMS [8].

There are very few studies with these devices that assess adherence to anticoagulant drugs. In the setting of VKA, Kimmel and cols [8] in a non-contemporary cohort of 136 patients find a percentage of 36% non-adherents, defined as missing > 20% of the doses. However, in this study the use of alternative pillboxes was allowed, and > 60% of the patients used the MEMS as a diary to record intakes and not as a dispenser, which can undoubtedly affect the results.

As far as we know, there are only two publications that evaluate adherence to DOACs using MEMS. Márquez-Contreras et al. found a percentage of taking adherence of 90.8% at six months with Rivaroxaban [19]. Recently Desteghe et al. [20] in an intervention study to improve adherence to DOACs using MEMS, found a percentage of 94.3% of taking adherence in the observation phase, very similar to our result (95,8%). In the study, daily telemonitoring increased the adherence proportion to 97.4%, and a telephone intervention in case of intake failure, increased it up to 99%, pretty similar to our VKA patients findings.

On the other hand, it has been suggested that a once daily regimen could improve adherence [21]. Nevertheless we have not found any difference in taking or schedule adherence between once versus twice daily regimen within DOAC group.

Traditionally, non-adherence has been considered as a dichotomous variable in the literature, considering as acceptable a taking adherence higher than 80% [7–12], but this is a totally arbitrary value. Some authors question this cut-off point if the evaluated pathology is serious, demanding an adherence even higher than 95% [20,21]. Recently, the Academic Non-Adherence Research Consortium encourages providing the adherence information of cardiovascular randomized trials, and proposes to refer it not as a dichotomous manner, but as a proportion of prescribed drug intakes [4].

In our study we found that TTR of patients taking VKA is greatly influenced by missed doses that have traditionally not been considered relevant. All patients who failed > 10% of the intakes have poorly controlled TTR (< 65%), as well as 73.3% of those who failed > 5% of the intakes. However, the perfect intake compliance does not guarantee

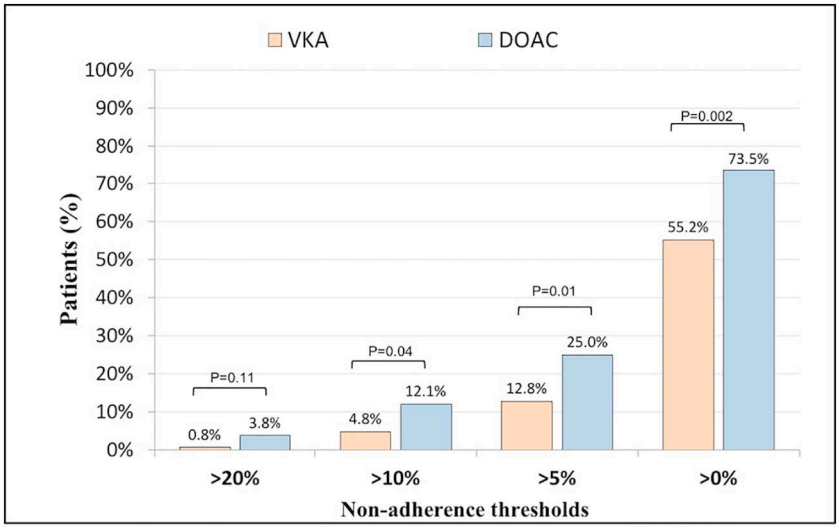

Fig. 3. Comparison of different non-adherence thresholds between VKA and DOAC groups.
VKA, vitamin K antagonists; DOAC, direct oral anticoagulants.

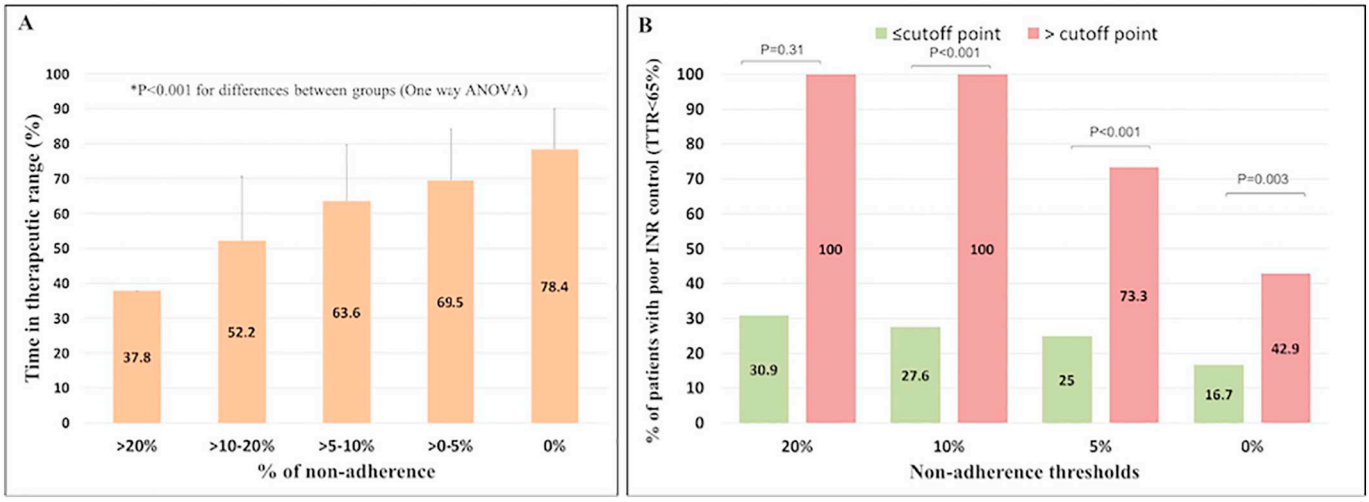

Fig. 4. A) TTR between different levels of non-adherence. Bars represent mean and standard deviation. B) Proportion of poor TTR control according to the non-adherence level.
TTR, time in therapeutic range.

Table 2
Events during follow up between VKA and DOAC groups. Results are shown as % (n/N).

	DOAC	VKA	p
Death	0.8 (1/132)	0.8 (1/125)	1
Stroke	3 (4/132)	1.6 (2/125)	0.68
Peripheral embolism	0.8 (1/132)	0 (0/125)	0.51
Stroke or peripheral embolism	3.8 (5/132)	1.6 (2/125)	0.45
ACS	1.5 (2/132)	0.8 (1/125)	1
Major bleeding	4.5 (6/132)	3.2 (4/125)	0.58
Intracraneal hemorrhage	0.8 (1/132)	1.6 (2/125)	0.61
Minor bleeding	12.9 (17/132)	14.4 (18/125)	0.72
Hospitalization for GI bleeding	2.3 (3/132)	0.8 (1/125)	0.63

ACS: acute coronary syndrome; GI: gastrointestinal.

an adequate control of the INR, since one out of every six patients who did not forget a single dose, had sub-optimal TTR.

The clinical relevance of non-adherence is evident in patients who missed > 5% of the intakes, with a higher risk for thromboembolic events during follow-up compared to those who failed < 5%. More studies are needed to ascertain if the difference in adherence to VKA versus DOAC affects the outcome to a similar extent.

4.1. Limitations

The sample size was calculated taking into account higher non-adherent proportions as described in the scarce literature available at the moment of designing the study. However, despite the high adherence found to both medications, without differences in 20% non-adherent patients, there were differences between the groups in terms of taking and schedule adherence, and in the proportion of 5% and 10% non-adherent patients.

VKA patients were under anticoagulation treatment for longer time, and this could represent a bias. Nevertheless, in our series this variable was not associated with adherence. All included patients were already under anticoagulant treatment per protocol. It may be reasonable to think that these patients have already been educated about the importance to medication adherence, so the generalization of the results to naïve patients could be limited. Nevertheless, an education program has not demonstrated utility in improving adherence in the setting of

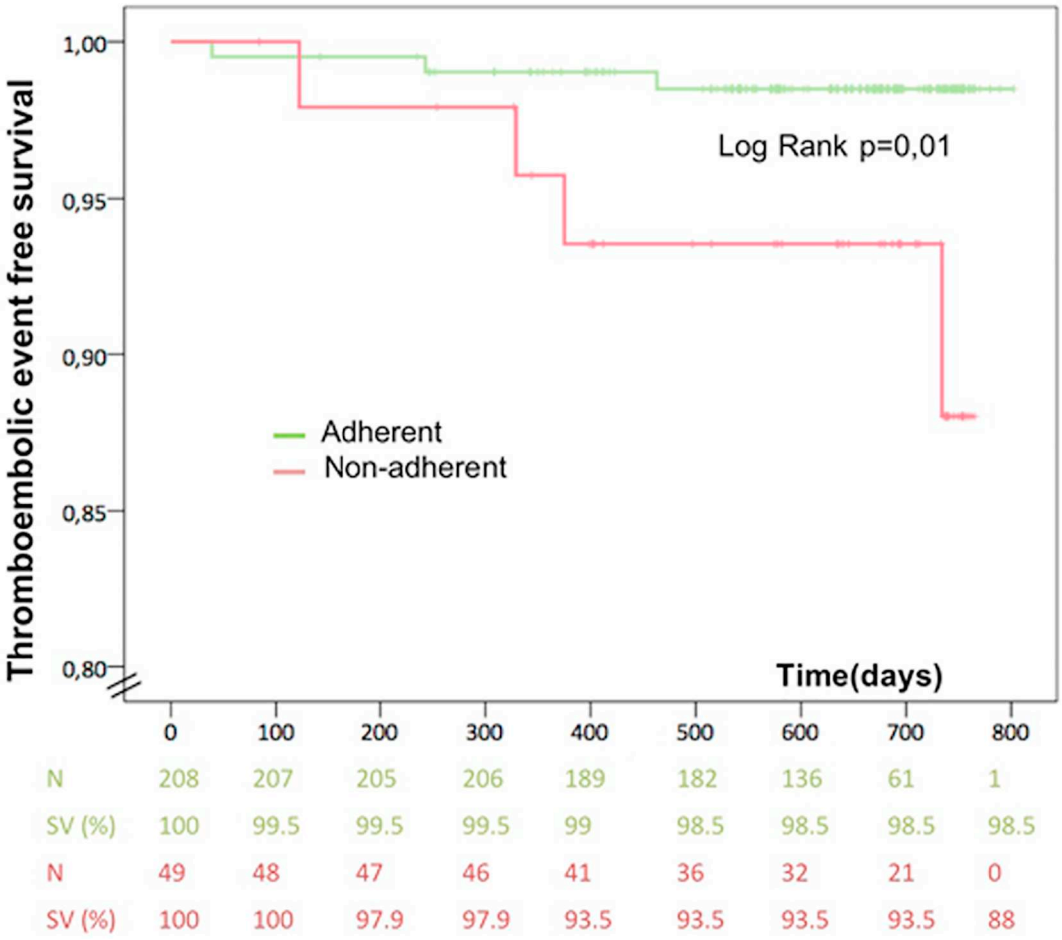

Fig. 5. Survival free of thromboembolic events taking a 5% non-adherence threshold.

DOAC treatment [22].

An intrinsic limitation of adherence studies is that the mere agreement to participate could represent a bias by selecting more collaborative and therefore more adherent patients. This might limit the generalization of our results to the rest of the population.

Finally, opening the MEMS does not exactly mean that the patient has taken the medication. So, the real compliance might have been overestimated. However, the MEMS system is still considered the gold standard for evaluating adherence [18].

5. Conclusions

In our community, adherence to anticoagulant drugs is excellent. Frequent contact with the healthcare system for INR controls may represent a reinforcement in VKA patients that can improve their adherence in comparison to those taking DOAC. TTR is very sensitive to even few missed doses and, as a non-adherence higher than 5% significantly increases the risk of thromboembolic events, the 20% cutoff point should not be accepted any longer.

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Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.04.023.

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