

## Safety profile of outpatient diagnostic catheterization procedures in patients under direct-acting oral anticoagulants



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### ABSTRACT

**Introduction and objectives:** Today it has become increasingly common to perform procedures without withdrawing oral anticoagulation. However, the need to withdraw oral anticoagulants prior to cardiac catheterization in patients chronically anticoagulated (OACs) remains controversial. We evaluated the efficacy and safety of performing transradial catheterization in outpatients without withdrawing direct-action oral anticoagulants (DOACs).

**Methods:** Prospective and observational study where 270 patients who underwent elective transradial cardiac catheterization were included from January 2013 through November 2017, divided into 3 groups of 90 patients based on their anticoagulant intake: group A (without OAC), with group B (with vitamin K antagonist), and group C (with DOACs), and matched according to the date of completion. In no case was the OAC discontinued before the procedure. We evaluated the complications of radial access within the first 24 h and 1 month after the procedure.

**Results:** The group of patients on DOACs had a higher proportion of men compared to the vitamin K antagonist group (71.1% vs 47.8%;  $P = .01$ ) and patients were younger in the group without OAC ( $63.45 \pm 11.47$  vs  $70.22 \pm 9.35$ ;  $P = .03$ ). Group B had a lower percentage of diabetic patients (22.2% vs 36.67% in group C,  $P = .03$ ). In group A, patients were more prone to having a history of ischemic heart disease compared to the groups of anticoagulated patients (27.84% vs 14.44% in group C,  $P = .028$ ) in addition to a more frequent intake of antiplatelet drugs. Radial access was the access of choice in most patients (98.2%). There were no significant differences when it comes to vascular access complications among the groups being the rate of hematoma and/or bleeding at discharge equal to 1.1% in the DOACs group and the arterial occlusion rates both at discharge and at 1 month between 0% and 2.2%.

**Conclusions:** In our experience performing transradial diagnostic cardiac catheterizations without discontinuation of DOACs is safe, with low rates of thrombotic and hemorrhagic complications, without any differences with vitamin K antagonist and no OAC.

**Keywords:** DOACs. NOACs. Direct vitamin K anticoagulants. Non-vitamin K anticoagulants. Cardiac catheterization. Transradial.

## Seguridad del cateterismo diagnóstico ambulatorio en pacientes en tratamiento con anticoagulantes orales de acción directa

### RESUMEN

**Introducción y objetivos:** Actualmente es cada vez más habitual realizar procedimientos sin retirar la anticoagulación oral (ACO), pero la necesidad o no de suspender la ACO antes del cateterismo cardiaco sigue siendo una cuestión controvertida. Se evalúan la eficacia y la seguridad de la realización de un cateterismo transradial en pacientes ambulatorios sin retirar los anticoagulantes orales de acción directa (ACOD).

**Métodos:** Estudio observacional, prospectivo, que incluye 270 pacientes sometidos a cateterismo transradial electivo desde enero de 2013 hasta noviembre de 2017, divididos en 3 grupos de 90 pacientes: grupo A (sin ACO), grupo B (con antagonista de la vitamina K), grupo C (con ACOD), emparejados según la fecha de realización del cateterismo. No se suspendió la ACO antes del procedimiento. Se evalúan las complicaciones del acceso radial en las primeras 24 h y un mes después del cateterismo.

**Resultados:** Había más varones tratados con ACOD que con un antagonista de la vitamina K (71,1 frente a 47,8%;  $p = 0,01$ ) y los pacientes eran más jóvenes en el grupo sin ACO ( $63,45 \pm 11,47$  frente a  $70,22 \pm 9,35$  años;  $p = 0,03$ ). En el grupo B hubo menos

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diabéticos (22,2 frente a 36,67% en el grupo C;  $p = 0,03$ ). En el grupo A, los pacientes tenían más antecedentes de cardiopatía isquémica que los pacientes con anticoagulación (27,84 frente a 14,44% en el grupo C;  $p = 0,028$ ), además de la toma concomitante de fármacos antiplaquetarios. El acceso fue radial en la mayoría de los pacientes (98,2%). No hubo diferencias significativas en las complicaciones del acceso vascular, con una tasa de hematoma o hemorragia al alta del 1,1% en el grupo con ACOD y tasas de oclusión arterial tanto al alta como al mes del 0-2,2%.

**Conclusiones:** En nuestra experiencia, la realización de un cateterismo diagnóstico transradial sin interrupción de los ACOD es seguro, con tasas bajas de complicaciones trombóticas y hemorrágicas, sin diferencias respecto a los pacientes en tratamiento con un antagonista de la vitamina K o sin ACO.

**Palabras clave:** ACOD. NACO. Anticoagulantes de acción directa. Anticoagulantes no antagonistas de la vitamina K. Cateterismo cardiaco. Transradial.

## Abbreviations

**BT:** bridging therapy. **COAC:** chronic oral anticoagulation. **DOAC:** direct-acting oral anticoagulants. **VKA:** vitamin K antagonists

## INTRODUCTION

The number of patients who receive chronic oral anticoagulation (COAC) is huge, and is expected to increase in the future due to the overall aging of the population and the increased incidence of conditions that will require COAC.

The prevalence of COAC among patients with coronary disease who undergo percutaneous coronary interventions is between 6% and 8%.<sup>1</sup> Most cases are due to the concomitant presence of atrial fibrillation with moderate-to-high embolic risk.

On the other hand, up to between 20% and 30% of the patients with atrial fibrillation and an indication of COAC present with coronary disease.<sup>2</sup> Taking into account that the prevalence of atrial fibrillation in the population is between 1% and 2%, up to 1-2 million anticoagulated patients in Europe will end up needing one coronary angiography procedure.

There is, therefore, a significant number of patients receiving COAC with vitamin K antagonists (VKA) or one of the most recent direct-acting oral anticoagulants (DOACs, Apixaban, Rivaroxaban, Dabigatran or Edoxaban) that require coronary angiography. The routine practice with these patients is very variable, but traditionally patients with COAC have discontinued the drug and moved on to bridging therapy (BT) with low molecular weight heparin a few days before and a few days after the procedure.<sup>3</sup> However, an increase of hemorrhagic events with this strategy in interventional procedures and higher morbidity and mortality in these patients due to bleeding or prothrombotic situations due to the discontinuation and reset of anticoagulants has been reported.<sup>2,4-7</sup>

The safety of diagnostic catheterization through radial access under treatment with acenocoumarol (VKA) has been demonstrated previously. In our group, the safety profile of VKA has already been evaluated in this type of patients in the past.<sup>8</sup> Since there is less evidence in patients on DOACs, with this work we want to provide new evidence on this regard, given the increasing number of patients anticoagulated with these new drugs over the last few years.

In this study, we report our experience and we evaluate the safety profile of transradial diagnostic cardiac catheterizations in patients on DOACs who were discharged the same day they

underwent the procedure. Also, we compared these patients with other treated with heparin during catheterization and patients on COAC with VKA.

## METHODS

### Study population

This is a prospective and observational study where 270 patients who underwent elective transradial cardiac catheterizations were included from January 2013 through November 2017, divided into 3 groups of 90 patients based on the intake of VKA, DOACs or without oral anticoagulant treatment, and then matched according to the date of completion. All patients who underwent diagnostic catheterization and were having DOACs during this period were recruited. As control groups, we decided to recruit the next patient who underwent a diagnostic catheterization without anticoagulant treatment and the next one that was receiving acenocoumarol without withdrawal.

In no case was oral anticoagulant therapy withdrawn prior the procedure.

In patients treated with DOACs, 20 were on dabigatran (22.22%), 38 patients on rivaroxaban (42.22%), 29 patients on apixaban (32.22%) and 3 patients on edoxaban (3.33%).

In patients undergoing VKA treatment with international normalized ratio (INR) values  $< 2$  (underdosing) and in DOAC patients who missed their last dose by mistake, intraprocedural sodium heparin was prescribed at a dose of 2500-5000 international units in one intra-arterial bolus. In our series, 21.3% of the patients treated with VKA received underdosing (INR  $< 2$ ) and, therefore, needed heparin. In this group of patients, the mean INR was  $2.5 \pm 0.06$ . The range was 1.3-4.3 (75% INR  $> 2.1$ ).

In a former article of our group<sup>8</sup> we described the methodology of outpatient catheterizations at our center that we detail here.

Patients without COAC received the standard anticoagulant therapy with one intraarterial bolus of 5000 IU of unfractionated heparin (the routine clinical practice at our center). Also, 2.5 mg of verapamil were administered intraarterially to all patients to prevent any radial spasms.

They underwent elective transradial cardiac catheterization with same-day discharge, after removing the compression bandage and achieving hemostasis. All cases were conducted through one hydrophilic 5-Fr sheath. Hospitalized patients who underwent diagnostic catheterization were excluded as well those in whom an angioplasty procedure was anticipated.

All procedures were conducted in a single interventional cardiology unit with huge experience using transradial access (over 90% of all cases annually) and with an active program of same-day discharge outpatient cardiac catheterizations.<sup>8,9</sup>

### Procedural characteristics

All patients are welcome at a room near the interventionalist laboratory and are evaluated by a nurse specialized in their monitoring and follow-up. This nurse is in charge of informing the patients, collecting the patient's background, verifying the doses and time of the last COAC intake, and estimating the INR in patients on acenocoumarol. After informing the patient and collecting the informed consent, the best vascular access is selected, assessing the quality of the pulse and performing the Barbeau test.

Once the procedure is completed, the radial compression is performed using the patent hemostasis technique for, at least, 2 h. Radial patency and possible complications are assessed in this room prior to the patient's discharge. The complications and outcomes of the vascular approach we assessed were: acute bleeding (with need to extend the length of compression), hematoma 5-10 cm at discharge, radial patency at discharge, bleeding and/or hematoma at 24 h, radial patency at 1 month and the presence of other unusual complications (pseudo-aneurysms, fistulas, arterial perforations, or compartment syndrome). For hematoma classification, the EASY criteria were used.<sup>10</sup> The compression of the vascular access was made with swab and elastic bands for 2 h using the patent hemostasis technique<sup>11</sup> where distal permeability is verified through plethysmography. Additionally, a 30 min extra-compression was performed if the puncture bled when the bandage was removed. In order to assess radial patency after the removal of compression, the test described by Barbeau et al. was used.<sup>12</sup> was used here. Artery occlusion was defined by type D response (no recovery of the curve of pulse in 2 min). All patients were contacted via telephone over the following 24 h after the procedure to determine delayed local complications, and they were all followed during 1 month to determine the access occlusion.

### Statistical analysis

Data are expressed as absolute rate and percentage for qualitative variables. Quantitative variables are expressed as mean (standard deviation) or median 25-75 interquartile range depending on variable distribution. Group comparisons were analyzed using the Student t test or its non-parametric equivalent; the Man-Whitney U-test for continuous variables, and chi-square test or Fisher's exact test were used for the categorical variables. Statistical significance was defined as *P* values < .05. The statistical analysis was conducted using the statistical package SPSS 19.0 (SPSS, Inc.; Chicago, Illinois, United States).

## RESULTS

The patients included in the study were assigned to three groups of 90 individuals each and matched by date of procedure: one

group without oral anticoagulation (group A), another group with anti-vitamin K treatment (group B) and another with direct-acting anticoagulants (group C).

The indication of oral anticoagulation in group B mostly corresponds to patients with atrial fibrillation (74.4%), 26.7% of patients had valvular disease and 5.6% of them were carriers of mechanical prostheses; the remaining patients received anticoagulation due to a past medical history of embolism (5.6%), dilated cardiomyopathy (1.1%) and other causes.

The baseline characteristics of our patients are shown on [table 1](#). The group treated with DOACs had a higher proportion of men than the VKA group (71.1% vs 47.8%; *P* = .01) and patients were younger in the group without oral anticoagulation (63.4 ± 11.5 vs 70.2 ± 9.3; *P* = .03). Group B had a lower percentage of diabetic patients (22.2% vs 36.67% in group C, *P* = .03). Group A patients had a past medical history of ischemic heart disease more frequently than the groups of anticoagulated patients (27.84% vs 14.44% in group C, *P* = .028) and therefore, they had undergone previous catheterization using the same access in higher percentages (20% group A vs 5.5% in group C, *P* = .04).

When it comes to the concomitant treatment with antiplatelet agents, patients without COAC took acetylsalicylic acid more frequently (72.2% vs 12.2%; *P* < .0005) compared to the DOACs group, as well as clopidogrel (23.3% vs 4.4%; *P* < .0005). Acetylsalicylic acid was also more widely used in the DOACs group compared to the VKA group (12.2% vs 3.3%; *P* = .048). All this is probably related to a greater suspicion of ischemic heart disease in these patients. There were only 2 patients treated with prasugrel and one with ticagrelor in the group without COAC.

There were no other significant differences on the remaining baseline characteristics (high blood pressure, dyslipidemia, body mass index, smoking...).

Radial access was the access of choice in most patients (98.2%), and ulnar access in the remaining patients. Regarding complications ([table 2](#)) of vascular access, during the procedure and during the 24 h and 1 month follow-up, there were no significant differences, showing a rate of hematoma and/or bleeding at discharge of 1.1% in the DOACs group and arterial occlusion rates both at discharge and at 1 month between 0-2 an 2% in this group. Only one patient needed hospitalization due to prolonged radial bleeding.

## DISCUSSION

The performance of diagnostic cardiac catheterizations without withdrawing COAC is recommended in the guidelines<sup>13</sup> and our standard routine here at our unit of hemodynamics and interventional cardiology is using mostly radial access (95%) excellent safety results.<sup>8,9</sup>

The information comes basically from studies conducted in patients under treatment with VKA. Two meta-analyses that addressed this issue<sup>14,15</sup> conclude that performing catheterizations without withdrawing COAC is safe and effective. The study published by the Finnish group led by Karjalainen<sup>16</sup> also assessed the safety profile comparing it to a group of patients on COAC and heparin BT. They found a rate of bleeding significantly higher in the latter group (1.7% vs 8.3%), being higher in the COAC-BT withdrawal group compared to the withdrawal group of COAC without BT (2.5% vs 8.3%). Also, if the procedure is done through radial access, the results in terms of bleeding are even better.<sup>17</sup>

**Table 1.** Demographic and procedural baseline characteristics

Variable	Total	Group A: no OAC (n = 90)	Group B: VKA (n = 90)	Group C: DOACs (n = 90)	P value
Age (years), median ± SD	68.59 ± 10.63	63.45 ± 11.47	72.09 ± 8.97	70.22 ± 9.35	.03 <sup>a</sup> NS <sup>b</sup> NS <sup>c</sup>
Men (%)	62.6	68.9	47.78	71.1	NS <sup>a</sup> .001 <sup>b</sup> .041 <sup>c</sup>
Hypertension (%)	75.9	83.33	67.78	76.67	NS <sup>a</sup> NS <sup>b</sup> NS <sup>c</sup>
Diabetes mellitus (%)	32.2	37.78	22.22	36.67	NS <sup>a</sup> .03 <sup>b</sup> .048 <sup>c</sup>
Dyslipidemia (%)	48.5	53.33	52.22	40	NS <sup>a</sup> NS <sup>b</sup> NS <sup>c</sup>
Smoking (%)	10	10	10	10	NS <sup>a</sup> NS <sup>b</sup> NS <sup>c</sup>
BMI (kg/m <sup>2</sup> ), median ± SD	30.10 ± 4.62	30.11 ± 4.45	29.22 ± 4.77	30.98 ± 4.51	NS <sup>a</sup> NS <sup>b</sup> NS <sup>c</sup>
Prior ischemic heart disease	17	27.78	8.89	14.44	.028 <sup>a</sup> NS <sup>b</sup> NS <sup>c</sup>
ASA treatment	79	65	3	11	< .0005 <sup>a</sup> .048 <sup>b</sup> < .0005 <sup>c</sup>
Clopidogrel treatment	25	21	0	4	< .0005 <sup>a</sup> NS <sup>b</sup> NS <sup>c</sup>
Prior catheterization same access (%)	11.5	20	8.89	5.55	.04 <sup>a</sup> NS <sup>b</sup> .031 <sup>c</sup>

ASA, acetylsalicylic acid; BMI, body mass index; DOAC, direct-acting oral anticoagulants; NS, non-significant; OAC, oral anticoagulation; SD, standard deviation; VKA, vitamin K antagonists.

<sup>a</sup> No OAC (group A) vs DOAC (group C).

<sup>b</sup> VKA (group B) vs DOAC (group C).

<sup>c</sup> DOAC (group C) vs groups A+B.

However, when talking about patients on DOAC treatment, the evidence is scarce and there is no consensus. The current guidelines on revascularization<sup>18</sup> do not include the recommendation of keeping oral anticoagulation during the procedure, but in recent expert consensus statements published by different international societies, there is controversy on this issue. Thus, due to the lack of existing evidence, the European document of antithrombotic consensus<sup>19</sup> recommends to not stop anticoagulation in the case of VKA, but pre-withdraw DOACs between 12 and 24 h (24-48 h in the case of dabigatran) in patients who will undergo the intervention. On the other hand, in the document on preoperative and perioperative antithrombotic management<sup>20</sup> they recommend to not withdraw antithrombotic treatment with DOACs in low-risk hemorrhagic procedures such as transradial diagnostic catheterizations because of its lower rate of vascular complications, especially when it comes to bleeding.

Despite all this, the standard practice with these patients is variable, but as a rule of thumb most hemodynamic laboratories worldwide withdraw COAC and move on to BT with low

molecular weight heparin a few days before and after the procedure.<sup>3</sup> However, there are more hemorrhagic events with this strategy when performing interventional procedures as well as more morbidity and mortality of these patients due to bleeding or prothrombotic situations that are created when withdrawing and resetting anticoagulant therapy.<sup>2,4-7</sup>

With the increasingly use of DOACs, new problems arise in our routine clinical practice when these drugs need to be withdrawn before performing procedures and it is common to see that in these patients BT is prescribed the same way as it is prescribed in patients undergoing VKA treatment from many medical and surgical specialties, although its use in recent consensus documents is not recommended.<sup>20</sup>

When it comes to cost-effectiveness, the BT strategy is a tremendous cost overrun due to several aspects: the higher incidence of hemorrhagic complications in patients who will need medical attention, the high cost of low molecular weight heparin, longer hospital stays, and the need to analyze the levels of anticoagulation

**Table 2.** Complications (bleedings and occlusions) and vascular access events

Variable	Group A: no OAC (n = 90)	Group B: VKA (n = 90)	Group C: DOACs (n = 90)	P value
Early bleeding or hematoma (%)	2.2	1.1	1.1	NS <sup>a</sup> NS <sup>b</sup>
Late bleeding or hematoma (%)	0	0	1.1	NS <sup>a</sup> NS <sup>b</sup>
Early occluded access (%)	3.3	3.3	2.2	NS <sup>a</sup> NS <sup>b</sup>
Late occluded access (%)	3	2.9	0	NS <sup>a</sup> NS <sup>b</sup>
Other complication (dissection, fistula, perforation)	0	0	0	

DOAC, direct-acting oral anticoagulants; NS, non-significant; OAC, oral anticoagulation; VKA, vitamin K antagonists.

<sup>a</sup> No OAC (group A) vs DOAC (group C).

<sup>b</sup> VKA (group B) vs DOAC (group C).

in patients under treatment with VKA. In other areas of interventional cardiology, progress has been made on this regard and cost-effectiveness studies have been conducted on this question, such as the study conducted by Coyle et al.<sup>21</sup> that showed that the non-prescription of BT saved US\$ 1800 per patient following some of the aforementioned aspects. Also, if we compare DOACs and VKA drugs, a recent study conducted by Shah et al.<sup>22</sup> in patients with permanent atrial fibrillation showed that all DOACs proved superior in a cost-effectiveness model that included quality-of-life adjusted survival, with dabigatran being the most cost-effective drug in patients with the highest thrombo-embolic risk of all.

The main conclusion that we can draw from this study is that it is safe to perform diagnostic cardiac catheterizations through transradial access in patients on chronic anticoagulation with DOACs. These patients do not have more frequent vascular or bleeding complications compared to those under standard therapy.

When it comes to bleeding complications, there was a low incidence rate in all groups without any significant differences. Another thing to take into consideration in the case of DOACs is the possibility of anticoagulation reversal with the specific antidote (currently only available for dabigatran and about to be on the market for factor Xa inhibitors) in case of serious complications which gives us a greater safety profile when performing invasive procedures with these drugs.<sup>23</sup>

In our population, the incidence of radial occlusion was exceptionally low in all groups. Early (< 24 h) and late occlusions (1 month) occurred in 2.2% and 0% of the patients from the DOAC group; in 3.3% and 2.9% of the patients from the acenocoumarol group compared to 3.3%; and in 3% of the patients from the heparin group without any statistically significant differences. Previous studies have reported extremely low rate of occlusions, even lower than 1%.<sup>24</sup>

We have not found in the medical literature any series similar to ours, although there are numerous series in which coronary angiographies are performed without withdrawing COAC with VKA, with results that are consistent with ours.<sup>8,25,26</sup>

There have been trials with DOACs in percutaneous coronary interventions that have not found any differences in the clinical adverse events (bleeding, embolism, ischemia) in patients in whom the percutaneous coronary intervention was conducted under different anticoagulation strategies.<sup>27,28</sup>

### Study limitations and future directions

The low incidence of complications and the small size of the sample did not allow us to conclude any significant statistical differences among the groups. It would be necessary that the size of the sample was larger, which is difficult in a single center. Maybe a multicenter registry could shed some more light on this issue.

Nowadays, the number of patients under acenocoumarol or warfarin treatment is rapidly dropping due to the exponential use of new anticoagulant drugs as dabigatran, apixaban, rivaroxaban, and edoxaban. In sum, new and larger studies on direct-acting oral anticoagulants should be conducted on this regard.

### CONCLUSIONS

The performance of outpatient diagnostic catheterizations using the radial access without withdrawing the DOAC treatment seems to be safe and does not bring a greater deal of complications compared to patients under treatment with acenocoumarol or without anticoagulant treatment. It would be advisable to conduct randomized studies to be able to confirm these data.

### CONFLICTS OF INTEREST

We declare no conflicts of interest whatsoever.

### WHAT IS KNOWN ABOUT THE TOPIC?

- Currently there is no consensus on the management of oral anticoagulation in patients taking direct-acting oral anticoagulants undergoing procedures such as diagnostic coronary catheterizations. In some centers anticoagulation is kept, resembling clinical practice in the management of antithrombotic therapy with heparin in some cases. Both the clinical practice guidelines and current consensus documents do not agree on what our approach should be with these patients since evidence is scarce.

## WHAT DOES THIS STUDY ADD?

- We believe that our study is of great interest for routine clinical practice, due to the growing use of direct-acting oral anticoagulants in all physicians' daily practice, including cardiologists and interventional cardiology. The use of these drugs has increased exponentially so it is not rare to find patients who are going to undergo a coronary angiogram who are taking DOACs. That is why we wanted to share the experience of our hemodynamic laboratory with this type of patients and show the efficacy and safety profiles of these drugs in this field.

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