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RESEARCH ARTICLE

KNOWLEDGE FROM A REGISTRY OF ORAL ANTICOAGULANT PRESCRIPTIONS KEPT BY CLINICAL PHARMACISTS IN A NEUROVASCULAR CARE UNIT: NEUROLOGIST PRACTICES AND THE WAY PHARMACISTS CAN SECURE PRESCRIPTIONS

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ABSTRACT

Two classes of oral anti-coagulant (OAC) are available to reduce the risk of ischemic stroke: vitamin K antagonists (VKA) and direct oral anti-coagulants (DOA). Our goals were to evaluate current prescription practices in a neurovascular care unit (NCU), to inform discharged patients on their drug and to follow them up. A registry of 124 patients with an OAC prescription, was kept by our clinical pharmacist team. Indications were analysed and patients got a pharmaceutical interview whenever possible. Several months later, pharmacists recorded benefice, adverse event and patient observance from the patient follow up consultation with a neurologist. Stroke upon atrial fibrillation mainly occurred (69%) and DOA were mainly prescribed (79%). Most of the patients (73%) were informed on their treatment before leaving. The registry allowed to follow 72% patients and showed an overall compliance (98%) and few thrombotic relapses (3%) or adverse effects (10%). Our registry showed that DOA prescription is significantly chosen over VKA for patients with stroke upon atrial fibrillation. Moreover, accompanying prescription of risky drugs, such as OAC, by clinical pharmacists, with personalised information prior to discharge, is feasible, likely contributing to increase patient adherence and safety of their treatment.

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INTRODUCTION

Neurovascular care units (NCU) are known to improve patient recovery from stroke (Drake *et al*., 1973; Rudd *et al*., 2005). Stroke management includes complication prevention and diagnosis to define the best treatment. Essentially, strokes have an ischemic or a haemorrhagic aetiology, occurring at a ratio of 9 to 1, respectively. The aetiological diagnosis leads to a specific medication to prevent recurrence. Arterial thromboembolic events are prevented by the use of oral anticoagulants (OAC).

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Atrial fibrillation (AF) is a very common heart dysrhythmia and highly generator of embolic event leading to severe blood clot events such as stroke. After a first stroke and the aetiology of AF established, anticoagulants are promptly introduced. Reference oral molecules used to be vitamin K antagonists (VKA): acenocoumarol, warfarine and fluindione. Recently, a new family of direct oral anti-coagulants (DOA) have emerged, including dabigatran, rivaroxaban and apixaban (Connolly *et al*., 2009; Patel *et al*., 2011; Granger *et al*., 2011). Oral anticoagulant molecules have demonstrated effectiveness in the prevention of thromboembolic events (Cove et Hylek, 2013). However, it is commonly accepted that patients have to collaborate with medics and paramedics in order to prevent severe side effects, especially haemorrhage, from his therapy

(Christensen et Lundh 2013; Heidbuchel *et al*., 2015). This new family of DOA obtained market authorisation five years ago in France and have been progressively all referenced in our hospital. Because of apparent advantages of the new DOA family compared to VKA, regarding food and drug interaction, therapeutic index and, more particularly, a lower risk of brain haemorrhage, physicians adopted rapidly these new molecules. This was suggested by the massive increasing sale of DOA from 1 million in 2009 to 117 million in 2013 of defined daily dose in France (ANSM, 2015). However, the bleeding risk remains present and little has been reported about the medical prescription practices. Moreover, no specific antidote is yet available. As previously reported, caution regarding the prescription should be taken and a follow up of the benefice and adverse effects is needed (Heidbuchel *et al*. 2015). We also believe that the pharmaceutical team can participate to these objectives.

In this study, current OAC prescription practices in a NCU were evaluated by keeping a registry of indication, patient age, renal function and whether prior treatment by OAC was taken or not. We also intended to tackle discharged patients with an OAC prescription to give them specific information by clinical pharmacists in order to increase patient compliance and therapeutic security. Then, we followed adverse effects, thrombotic relapses and patient compliance.

MATERIALS AND METHODS

Population sample

The present prospective study was conducted through an 18 months period of time, from January 2nd, 2013 until July 18th, 2014 in a 26 beds-NCU. A hundred and twenty four patients had an OAC prescription during this study. This work has been approved by our institutional review board.

OAC available in the drug reference list of our hospital

All VKA molecules available on the market are referenced in our hospital since at least 2010. However, acenocoumarol, which is the least used in France, was absent from the prescriptions of the NCU in this study. Among the DOA molecules, only dabigatran and rivaroxaban were present in the drug references list of our hospital at the time of our study. Therefore, apixaban, which was referenced in our hospital in June 2014, was missing from this study.

Prescription analysis

The pharmaceutical team is in charge of the analysis of hospital prescriptions. The information system used in our hospital is Orbis® (Agfa Healthcare). Orbis software contains many interfaces among which, the pharmaceutical validation of prescriptions and the electronic patient records (EPR), including medical letters and biological results. The Table 1 synthesises the required posology of OAC depending on patient age and renal function. The creatinine clearance was estimated using the equation of Cockroft and Gault (Cockcroft et Gault 1976).

Patient counselling

At discharge, patients with OAC treatment were given an interview with a clinical pharmacist of approximately thirty minutes reviewing their medication: indication, proper use and awareness of the bleeding risk and how to prevent and identify a potential bleeding and advices on self-medication because of drug interaction. Educational materials used were (i) a patient information leaflet and (ii) a patient alert card specific of the prescribed OAC. The VKA notebook given can be viewed in a report from the French National Agency for the Safety of Medicines and Health Products (ANSM) (ANSM, 2015). Specific rivaroxaban and dabigatran leaflets in the secondary prevention of stroke in patients with non-valvular AF were made by pharmaceutical and medical teams and were previously described (Cyrus *et al*. 2015).

Patient follow-up

We kept records of OAC prescriptions in a patient registry. We recorded (i) the indication, (ii) whether it was a first or an on-going prescription of OAC, (iii) whether a switch of molecule took place during hospitalisation and (iv) whether they benefited a medication review with a pharmacist. Generally, a routine medical consultation with a neurologist was planned 1 to 6 months afterwards. The physician ensured tolerance and efficiency of the OAC treatment, as well as patient compliance and then, he decided to pursue or not the prescription. We used the Orbis® software and looked into the medical report of this consultation to fill in our follow up registry with four items: (i) serious adverse effect, (ii) non-serious adverse effect, (iii) thrombotic relapse and (iv) compliance. Serious side effects and thrombotic relapses were known from hospitalisation or medical files. Patients themselves reported non-serious side effects and compliance, which could only be objectively verified if VKA was taken using their INR results.

Statistical analyses

Means were calculated ± standard error of the mean (sem) using the GraphPad Prism® software. Proportions were compared using the Chi-2 squared test as appropriate (effective population size >5) or using the Fisher's Exact Test (effective population sample <5) using Biostatistical on line R software approved by INSERM accessed on Biostat TGV. Results were considered significantly different if $p<0.05$ (*), $p<0.01$ (**) or $p<0.001$ (***).

RESULTS

Population characterisation

The studied population sample consisted in 124 patients (Table 2). We registered the leading cause of hospital admissions and the corresponding indication of OAC prescription (Table 3). As expected in a NCU, most patients were treated for cardioembolic stroke prevention (78%), while 22% patients were treated for a thrombotic event whether the consequence was a stroke or not. AF was the first cardiac cause of stroke (68%). Cardiac genetic defect (atrial septum abnormalities, interauricular communication and ventricular aneurysm) was

the second cause of stroke representing 5% of all indications. Of note, four patients were on OAC for a stroke upon AF, but were hospitalised for another reason: epileptic crisis (x 2), risperidone intolerance and anxiety. Three of them were on DOA and were not switched to another OAC. However, the fourth patient who came for lack of compliance regarding his anti-epileptic treatment was switched from VKA to DOA in order to increase patient observance (not shown).

Prescription analysis

In order to analyse neurologist practices in our NCU, distribution of the OAC class prescription was analysed. DOA were significantly more prescribed than VKA and accounted for 64% of the total OAC prescriptions (Fig. 1A). Dabigatran and rivaroxaban were the two molecules the most prescribed (32% each) (Fig. 1B). A quarter of the prescriptions was in favour of fluindione (25%) and warfarine represented 10% of prescriptions. The only indication of dabigatran was the prevention of stroke in non-valvular AF patients. Rivaroxaban was also used in the treatment of deep vein thrombosis (DVT) for 6 out of 9 patients. Within the VKA family, fluindione was 2.5 times more prescribed than warfarine (Fig. 1B).

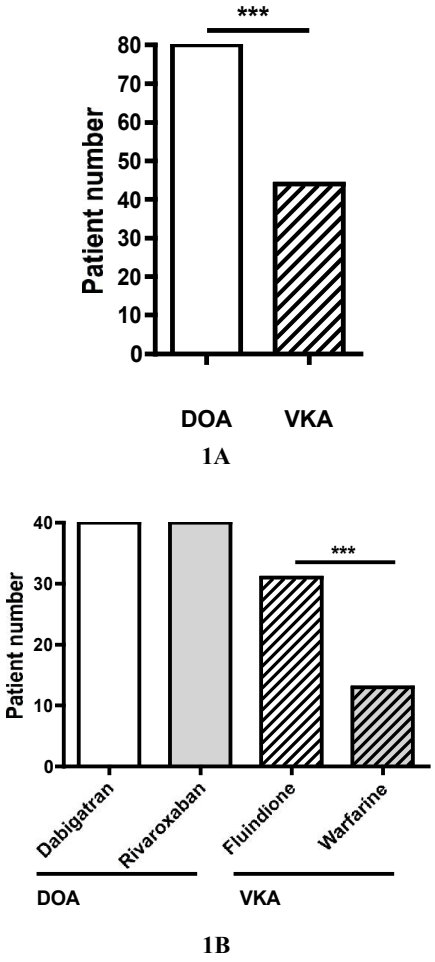

Figure 1. Distribution of oral anti-coagulant prescriptions in the neurovascular care unit. 1A, Distribution of oral anti-coagulant classes prescriptions: direct oral anti-coagulant (DOA) and vitamin K antagonists (VKA). **1B**, Distribution of the four oral anticoagulants prescribed in the neurovascular care unit among the population sample.

VKA were prescribed essentially when the stroke aetiology was different from a stroke in non-valvular AF patient, such as other than AF cardioembolic cause, occlusion following artery dissection and cerebral thrombophlebitis (not shown). Eighty percent of patients underwent a primo-prescription of OAC, whereas 20% of patients (n=26) had a thrombotic event while on OAC or anti-platelet medication (Table 4). No switch was made in seven cases where treatment was appropriate and no alternative could be suggested even with a low INR. These patients were reminded the importance of following their treatment by physicians but also by our pharmaceutical team. For one patient, aspirin was added to dabigatran. When previous treatment was considered to be inefficient a switch was made (n=19). In one case, aspirin was co-prescribed with a VKA. Strikingly, the major switch observed was from VKA to DOA for people with stroke upon AF, whether the INR was in the correct window or not (11 out of 21). Of note, in some cases, a VKA was preferred for a specific reason, such as patient refusal to be on DOA, absence of antidote or necessity to follow efficiency (not shown).

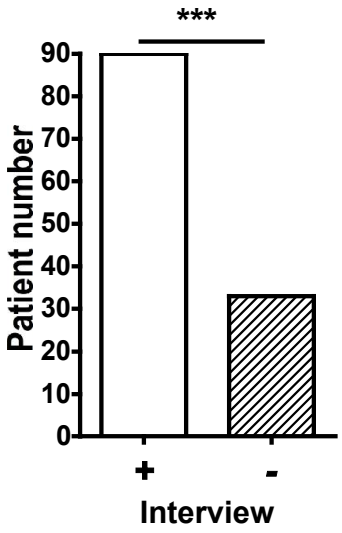

Figure 2. Patients informed or not on the oral anti-coagulant treatment before leaving hospital. Patients had an interview with a pharmacist (+: n = 90) or not (-: n = 34). Distribution of the 34 patients who were not informed before leaving was as followed: 17 patients were out of the care unit, 16 patients were cognitively impaired and one patient refused to discuss with a pharmacist.

While VKA dosage depends on INR, DOA dosage needs to be adapted to patient age and renal function. Hence, our clinical pharmaceutical team validated that DOA posology was in aggreement with recommendations summarised in Table 1 (not shown). In few cases, patients received a lower or a higher dose than the recommended dose. Neurologists prescribed a lower posology when they estimated that patient was at higher risk of side effects such as bleeding transformation of stroke leading to a cerebral haemorrhage. On the other side, when physicians gave a higher posology, they also gave a prescription of blood creatinine measurement to ensure that their renal function would promptly recover. In both cases, posology adaptation took place one month later. At last, in agreement with a contraindication of DOA in case of severe renal insufficiency, VKA were prescribed to patients with creatinine clearance below 30 $mL.min^{-1}$.

Table 1. Posology recommendations for two direct oral anti-coagulant molecules and vitamin K antagonists according to patient age and renal function

	DOA		VKA
Characteristic	Dabigatran	Rivaroxaban	
Age			
< 75 years	150 mg bid	20mg qd	Authorised
> 75 years	110-150 mg bid	20mg qd	Caution
> 80 years	110 mg bid	20mg qd	Caution
Creatinine clearance			
> 50 mL.min^{-1}	150 mg bid	20 mg qd	Authorised
30- 49 mL.min^{-1}	110 mg bid	15 mg qd	Authorised
15- 29 mL.min^{-1}	Contraindicated	15 mg qd	Authorised
< 15 mL.min^{-1}	Contraindicated	Not recommended	Caution

DOA, direct oral anti-coagulant; VKA, vitamin K antagonists.

Table 2. Population sample characterisation

Population characteristics n = 124	
Male, n (%)	66 (53)
Mean ± sem. age, yr	73 ± 7.8
Mean ± sem. creatinine clearance, mL.min^{-1}	77 ± 25

sem, standard error of the mean.

Table 3. Indication for the prescribed oral anti-coagulants in the neurovascular care unit

Indication	No. (%) Patients
Stroke upon atrial fibrillation	85 (68)
First prescription	59
Recurrent stroke while on OAC	19
Stroke while on aspirin	2
Other hospitalisation reason	4
Primary prevention of stroke	1
Other cardioemboligen-caused stroke	12 (10)
PFO-ASA	4
Interauricular communication (PFO)	1
Ventricular aneurysm	1
Cardiac insufficiency	5
Undetermined	1
Venous thromboembolism	15 (12)
Cerebral thrombophlebitis	6
Deep vein thrombosis	9
Artery dissection-caused stroke	7 (6)
Carotid artery dissection	4
Cervical artery dissection	2
Aortic artery dissection	1
Other cause of stroke	5 (4)
Hypertensive thrombotic microangiopathies	1
Dissecting aneurysm of basilar artery	1
Thrombosis on an intracerebral aneurysm-embolised coil	1
Atherothrombosis plaque with mobile intra-aortic debris	1
Uncertain aetiology	1

OAC, oral anti-coagulant; PFO-ASA, patent foramen ovale (PFO) and atrial septal aneurysm (ASA).

Table 4. Therapeutic decision made for patient with cerebral stroke while on oral anti-coagulant or anti-platelet treatment

Primary indication	Prescription change	Observations	No. Patients
Stroke upon AF (n=21)	No switch of OAC (n=5)	Rivaroxaban	2
		Dabigatran: baby aspirin added	1
		Fluindione: INR was below the target window (one had a prosthetic valve)	2
	Switch within DOA class (n=1)	Rivaroxaban /Dabigatran: rivaroxaban was not efficient	1
	Switch VKA /DOA (n=11)	INR within the target value: VKA was not efficient	6
		Low INR (n=4) or compliance problem (n=1) to increase the therapeutic index	5
	Switch DOA /VKA (n=2)	Stroke upon AF: DOA was not efficient	1
		Stroke upon AF: DOA was not efficient + atheroma context	1
	Switch aspirin / DOA (n=2)	Patient did not tolerate VKA and was only on aspirin	1
		Recurrent stroke	1
Other cause of stroke (n=4)	No switch of VKA (n=1)	Fluindione: hypertensive thrombotic microangiopathies: INR was low	1
	Aspirin / VKA switch (n=2)	Dissecting aneurysm of basilar artery	1
		Uncertain aetiology	1
	VKA added to previous aspirin treatment (n=1)	Thrombosis on an intracerebral aneurysm-embolised coil	1
VTE (n=1)	No switch of VKA (n=1)	Fluindione: cancer aetiology	1

AF, atrial fibrillation; DOA, direct oral anti-coagulant; INR, international normalised ratio; OAC, oral anti-coagulant; VKA, vitamin K antagonists; VTE, Venous thromboembolism.

Table 5. Patient on oral anti-coagulant follow-up

Follow up	No. (%) patients		VKA vs. DOA P Value	No. (%) total Patients (n=89)
	VKA (n = 34)	DOA (n = 55)		
Serious adverse effect[a]	0 (0)	2 (3.64)	0.522	2 (2)
Non serious adverse effect[b]	0 (0)	9 (16.36)	0.012	9 (10)
Thrombotic relapse	2 (5.88)	1 (1.81)	0.555	3 (3)
Compliance	33 (97.06)	54 (98.18)	1	87 (98)

DOA, direct oral anti-coagulant; VKA, vitamin K antagonist.
[a]Serious adverse effects were: subarachnoid haemorrhage and menorrhagia.
[b]Non serious adverse effects were: five minor bleeding, two gastrointestinal symptoms, one bad tolerance and one diminution of the prothrombin time.

Pharmaceutical interview and OAC registry

In order to ensure patient adherence and safety of their medical treatment, our clinical pharmaceutical team seeks to inform outgoing patients on the changes in their medication. As shown in Figure 2, we managed to inform 73% of patients leaving the NCU with an AOC prescription. Therefore, we investigated why more than a quarter of outgoing patients (27%) could not have an educational interview. Among the 34 patients not seen, (i) 17 patients (50%) were missed because of time schedule problems, e.g. they had already gone home or were undergoing an exam, representing 14% of total patients; (ii) 16 patients (48%) would not understand us for cognitive or language reasons and (iii) one person (2%) refused the interview (not shown). Outgoing patients had a systematic follow up appointment with a neurologist 1 to 6 months after hospitalisation. This consultation was important especially when it was a first prescription of OAC or if a switch among the OAC classes was made. Eighty-nine patients came back to the hospital for this appointment or were hospitalised again. We looked into the medical letter in their EPR to note tolerance, efficiency and global observance (Table 5). Firstly, a serious bleeding occurred for 2 patients under DOA and none was observed for patients under VKA. For the first patient who presented a subarachnoid haemorrhage, it appeared that it was due to a haemorrhagic conversion of ischemic stroke and a DOA introduction done too early. The DOA was stopped, and reintroduced a few days later, when safer. For the second patient, menorrhagia with a drop of haemoglobin concentration occurred. A uterus fibroma was diagnosed and surgically removed, after which the patient was prescribed the same DOA medication. Secondly, non-serious adverse effects were reported in the DOA group only and accounted for 16% within the DOA group. Among these side effects, 5 out of 9 were minor bleeding, which did not lead to discontinuation of therapy. Other side effects were: digestive troubles (n=2), bad tolerance and a diminution of the prothrombin time. A switch to VKA was made in the last 2 cases.

Treatment inefficiency, illustrated by a thrombotic relapse, was monitored in 3 patients: 2 under VKA and 1 under DOA. One patient under VKA had regular thrombotic recurrence because of a vertebrobasilar dolichoectasia. An uncontrolled INR was found to be the cause for stroke recurrence for the other patient. He was then switched from fluindione to warfarine, which has a longer half-life time. The third patient had another stroke, because its DOA had been stopped for a prostate surgery and had never been restarted afterwards. At last, overall compliance was reported, with only two patients stating difficulties to be compliant (regardless the type of OAC).

DISCUSSION

The two classes of OAC share indications, which are (i) primary or secondary stroke prevention in patient with risk factors such as non valvular AF and (ii) treatement of VTE. Although there is no recommendation to choose DOA over VKA, our study shows that DOA were preferred by neurologists in both indications. These medical practices are supported by previous findings showing that DOA and VKA have the same bleeding profile side effects in patient with AF, but DOA appear to be easier to use for a lifespan treatment (O'Dell, Igawa, et Hsin 2012). Similarly, DOA seemed to be more convinient with a safer bleeding risk for the treatment of DVT (Wu *et al*., 2014; van Es *et al*., 2014). Patients who had cardioembolic stroke, but a prosthetic valve or no AF, were not eligible for DOA and received a VKA prescription. Indeed, these latter conditions have not been tested in DOA clinical trials, probably because they are less frequent. However, it has been established that patients with heart prothesis valve should not be given a DOA over a VKA (Eikelboom *et al*., 2013).

Despite the cost of an INR follow up with VKA, DOA tend to be more cost-effective than VKA because of the renal function monitoring, but most importantly of their price itself (Freeman *et al*., 2011). However, considering the fewer major bleeding risks with DOA, these two classes of OAC have to be evaluated during an extra several years in order to get a better idea of their pharmaco-economic impact. Dabigatran and rivaroxaban were equally prescribed over the studied time period, suggesting that neurologists favoured none of them. However, only rivaroxaban was prescribed to treat DVT because it is reimbursed by the French social security, whereas dabigatran is not yet reimbursed (Haute Autorité de Santé, 2015; EINSTEIN Investigators *et al*., 2010). Of note, apixaban is referenced in our hospital since June 2014. This molecule is now prescribed in the NCU at first or second intention for older people or with low weight or with atherosclerosis plaques (data not shown). These prescriptions are in agreement with Harenberg and colleagues who reported *via* a meta-analysis that apixaban and dabigatran may offer the best benefit-risk balance for stroke prevention in non-valvular AF patients (Harenberg *et al*., 2012). Between VKA molecules, fluindione was more prescribed than warfarine, even if warfarine could be easier to equilibrate because of its longer half-life time: 35 to 45 hours *versus* 31 hours for fluindione. These proportions correlates with general French practices, since fluindione was 6 times more prescribed than warfarine in 2013 (ANSM, 2015).

Among 20% of recorded patients who had a stroke while on anti-coagulant or anti-platelet therapy, different switches were

adopted. The observed therapeutic options matched to those previously described (Touzé and Ciocanu 2014). When a non-valvular AF caused the stroke, a majority of switch from VKA and from aspirin to DOA was observed (13 patients out of 18 e.g. 72%). Actually, a meta-analysis demonstrated that the overall major bleeding was slightly reduced with DOA, compared to VKA, and most importantly, DOA exposed to a significantly lower risk of intracranial haemorrhage (Connolly *et al*., 2009; Patel *et al*., 2011; Ruff *et al*., 2014). Moreover, a French registry, including 17410 patients on VKA who were switched or not to a DOA molecule, reported no increase in major bleeding or in ischemic stroke in patients switched to a DOA compared to patients maintained on VKA during the 10-months period of follow up (Bouillon *et al*., 2015). These results support the safety and efficacy of a DOA switch in real-world conditions. At present, no recommendation on the therapeutic attitude has been published, since the molecule choice depends on the clinical context. Importantly, it has been pointed out that patient education in case of weak observance could be the key for continuation more successfully (Christensen et Lundh 2013; Heidbuchel *et al*., 2015). Moreover, the ageing population found in the NCU means that patients could have various pathologies with corresponding multi drug treatments. Therefore, clinical pharmacists in NCU help verify drug dosage adaptation and potential drug interaction. Moreover, patients welcomed our team to explain their medications, helping to increase compliance and drug safety and efficiency.

Two major bleeding occurred in the DOA population during the time period of follow up and none in the VKA group. However, our sample of 89 followed up patients is too small to make any meaningful comparison and we have to look into specific patient cases. For two patients, their OAC treatment was pursued after the bleeding aetiology being under control (haemorrhagic conversion of ischemic stroke and uterus fibroma). Actually, no difference in major bleeding occurrence between patients on VKA or DOA has been reported in the literature in real-world conditions. Indeed, a recent and comprehensive pharmacovigilance study followed severe haemorrhage incidence in patients taking rivaroxaban (Tamayo *et al*., 2015). Consistently with the ROCKET essay (Patel *et al*. 2011), Tamayo and colleagues showed, that older patients or with comorbidity, were more likely to develop a major bleeding. Moreover, in a German registry of 1776 patients with AF on rivaroxaban, major bleeding occurred in proportion that was not higher than that reported with VKA (Beyer-Westendorf *et al*., 2014). From our study, it appeared that patients in the DOA group reported more minor side effects than the VKA group. Two side effects led to a switch of therapy, reminding the importance of having a large drug panel convenient for all particular patients. Yet, no difference in (Patel *et al*., 2011) or less (Connolly *et al*., 2009) major and minor bleedings were reported with rivaroxaban and dabigatran, respectively, compared to warfarin. These discrepancies with the RE-LY and ROCKET investigations are probably due to our small population sample and shorter studied time period. Also, fluindione was the most prescribed VKA in the NCU studied. As reported in the literature (Connolly *et al*. 2009), we found that patients under dabigatran were more exposed to gastrointestinal symptoms.

Three thrombotic relapses occurred between the 89 followed-up patients under anti-coagulant treatment. One patient had a highly pro-thrombotic pathology, vertebrobasilar dolichoectasia, while another patient had an INR below the therapeutic window. In the third case, DOA was actually not taken because its prescription had not been restarted after prostate surgery. A better efficiency was previously reported when using dabigatran (Connolly *et al*., 2009) or rivaroxaban (Patel *et al*., 2011), compared to warfarin. Although the difference was not significant and fluindione was more used than warfarine in the VKA group, our findings tend to confirm these results. This difference between the two classes may be due to difficulties in equilibrating INR for certain patients.

Our study highlights some known problems: (i) regarding VKA: the difficulty to get the INR in the therapeutic window and (ii) regarding the DOA: the minor side effects seemed to be more important than for VKA and (iii) the problem of coordinating properly patient care, such as for old patients being treated for several pathologies and the resulting omission of one treatment. Moreover, our study revealed neurologist practices in a NCU, regarding the use of the new OAC class, DOA. Although patient education of these critical drugs remains essential and pharmacists contribute to it, they are not present enough in care units, leaving too many patients not informed. Our work is in line with national and European recommendations to keep a close watch on major bleeding risk in patients receiving a new prescription of OAC. Though our registry was limited in time and case numbers, it still lights up real-world conditions of clinical practices, and show how clinical pharmacists can help securing OAC prescriptions.

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