

## Observational Study About Old Patients with Non-Valvular Atrial Fibrillation in Direct Oral Anticoagulant Therapy

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### Abstract

**Background:** Atrial fibrillation is the most frequent cardiac arrhythmia, with a prevalence of approximately 1.5 to 3% in adults but greater in older people, that have often been under treatment or untreated or worse treated aspirin. Compared with VKA, DOACs have shown a favorable risk-benefit. The aim of this study was to assess the efficacy and safety of DOACs in patients older than 74.

**Materials and Method:** From March 2013 to June 2017, 667 patients older than 74 affected by non-valvular atrial fibrillation were followed in cardiology department of Maria Vittoria Hospital of Turin, Italy. Everybody controlled blood test as indicated by EHRA guidelines.

**Results:** 283 (42%) were male; 384 (58%) female. Mean age was 88 years (range: 75 - 98). Mean CHA2DS2-VASc and HASBLED were respectively 4,57 and 2,46. 123 patients were lost to follow up and 9 dead for not related causes. During the follow up, 639 days/pt, we saw one recurrent deep venous thrombosis in a patient with poor compliance; one brain ischemic attack; 6 major bleeding; 3 acute coronary syndromes. Patients taking VKA (followed by transfusion centre) had a bleeding incidence of 1,54/100 pt for year.

**Conclusion:** The conclusions of our dedicated clinic experience are in agreement with the literature: scarce side effects, lower the percentages of major events and low proportion of substitutions/suspension of the therapy. The DOAC dedicated clinic improved compliance, adherence, was liked by patients and doctors, without additional substantial costs for the national health system. The bleeding risk reduction was statistically significant ( $P < 0,05$ ). Nobody had intracranial hemorrhage.

**Keywords:** Atrial Fibrillation; Anticoagulant Therapy; Direct Oral Anticoagulant

### Abbreviations

VKA: Vitamin K Antagonists; DOAC: Direct Oral Anticoagulant; NOAC: New Oral Anticoagulant; DAPT: Dual Antiplatelet Therapy; AF: Atrial Fibrillation; CKD: Chronic Kidney Disease; VTE: Venous Thrombo-Embolism; TTR: Time in Therapeutic Range

### Introduction

Atrial fibrillation is the most frequent cardiac arrhythmia, with a prevalence of approximately 1.5 to 2% in the general population in developed countries. By 2030, 14 - 17 million AF patients are anticipated in the European Union, with 120,000 - 215,000 newly diagnosed patients per year [1-3]. Estimates suggest an AF prevalence of approximately 3% in adults aged 20 years or older [4,5] with greater prevalence in older people [6]. This disorder is associated with a high mortality, morbidity and impairment of quality of life [7]. Many AF patients present at older age (e.g. 75 or 80 years). There are no studies suggesting that cardiovascular risk reduction is less effective

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in these 'elderly' AF patients than in younger patients. Older patients have been often under treatment with VKA or untreated or worse Aspirin-treated.

Patients at older age may present with multiple comorbidities including dementia, a tendency to falls, CKD, anemia, hypertension, diabetes, and cognitive dysfunction. Such conditions may limit quality of life more than AF-related symptoms. Impairment of renal and hepatic function and multiple simultaneous medications make drug interactions and adverse drug reactions more likely. Integrated AF management and careful adaptation of drug dosing seem reasonable to reduce the complications of AF therapy in such patients. Since 2009 four products have been approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) and are available to prescribers: rivaroxaban (Xarelto®, Bayer), apixaban (Eliquis®, Pfizer), dabigatran (Pradaxa®, Boehringer-Ingelheim) and edoxaban (Lixiana®/Savaysa®, Daiichi Sankyo). Their efficacy and safety have been assessed in large phase III trials and in real world data. Compared with vitamin K antagonists (VKAs), DOACs have shown a favourable risk-benefit profile in patients with atrial fibrillation or VTE [8-11]. The aim of this study was to assess the efficacy and safety of DOACs in elderly patients (aged 75 years or more) with atrial fibrillation.

### Materials and Methods

#### Patients

From March 2013 to June 2017, 1014 patients affected by non-valvular atrial fibrillation were followed in cardiology department of Maria Vittoria Hospital of Turin Italy. Of theme, 667 were older than 74. The term valvular AF is used to imply that AF is related to rheumatic valvular disease (predominantly mitral stenosis) or mechanical prosthetic heart valves [12]. In fact these patients were excluded from the study. Patients treated with dronedarone were excluded, and rarely DOAC was used in patients with biological prosthetic valve. The dose was reduced for dabigatran if the patient was older than 80 years, or renal function was reduced (calculated creatinine clearance 30 - 50 mL/min). For rivaroxaban the dosage was reduced to 15 mg once a day if calculated creatinine clearance was 15 - 49 mL/min. The low dose of apixaban 2,5 mg twice a day was used if the patient has almost two of these parameters, age major of 80 years, reduced calculated creatinine clearance (15 - 29 ml/m) or body weigh lower than 60 Kg [13].

#### Methods

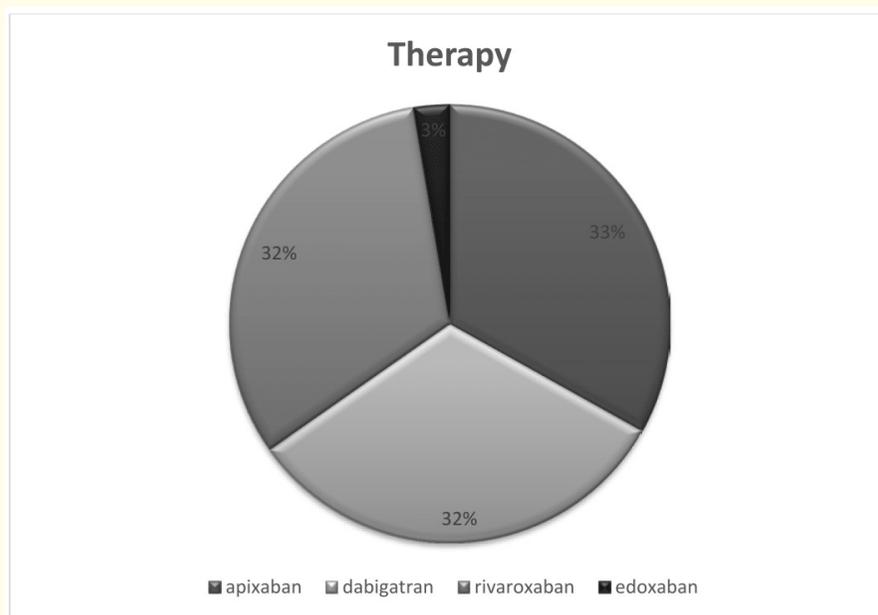
All patients underwent to blood test with evaluation of baseline hemoglobin, liver and kidney function. In all patients thromboembolic and bleeding risk were calculated. The new therapy was started when INR was < 2. Patients were investigated for evaluate the presence of hypertension, ischemic heart disease, congenital heart disease or other conditions such as pericarditis or hyperthyroidism or if the fibrillation was in healthy heart . All patients were invited to control blood test at 1°, 3°,6°,12 months as indicated by EHRA guidelines [14]. EHRA guidelines propose a uniform card to be completed and carried by each patient in which were marked the DOAC used, the other drugs that the patient assumed, the baseline value of hemoglobin liver and renal function. We gave the patients some tables containing information about drug-drugs interaction, a indication in case of planned surgery to explain how to stop DOAC in according to hemorrhagic risk of surgical intervention, renal function and the DOAC utilized, a scheme indicating when the NOAC may be started after stopped the VKA or a parenteral anticoagulant and the time of blood test control. A nurse role was to help patients in difficulties about dosing error, in taking the drugs, in drug-drug interaction, mild bleeding, surgical procedures, and in understanding the tables (how shifts from VKA).

### Results

283 (42%) are Male 384 (58%) Female. Mean age was 88 years (range: 75 - 98). Mean CHA2DS2-VAsc was 4,57 and mean HASBLED was 2,46. In females the HASBLED score was a little higher than in male and the opposite was for the CHADSVASC score. Forty-five % had paroxysmal atrial fibrillation and 55% permanent or persistent. 220 patients (33%) started dabigatran, 165 (75%) assumed low doses, in 227 patients (34%) we prescribed apixaban, 172 (76%) with low dose, in 202 patients (30,3%) rivaroxaban was administered, 158 (75%) at low doses and 18 (2,7%) patients received edoxaban, 10 (55%) at low dose. 61% of patients were naïve and 39% shifted from

VKA from VKA to DOAC for adverse effects of warfarin or because they wished change the therapy or TTR (time in therapeutic range) was insufficient to protected them. Their TTR medium was 54.55 patients assumed also cardioaspirin, Nobody was in DAPT at the beginning of DOAC therapy but 3 patients had coronary acute syndrome and shift to VKA, only one restarted apixaban low dose. During the follow-up, 639 days/patient, 9 patients dead for not drug related causes. The vast majority of patients were hypertensive (82%), someone (15%) had mild renal dysfunction, and chronic ischemic disease (21%) and 20 patients presented a lone atrial fibrillation. The most frequent side effect was stomachache and dyspepsia in patients in dabigatran that led to shift to another drug .We see a recurrent thromboembolic event (deep venous thrombosis) in a patient with poor compliance, 6 major bleeding, one in a patient in apixaban, for colon cancer, one gastro intestinal bleeding in a patient assuming dabigatran and two gastrointestinal bleeding in rivaroxaban. In one patient dabigatran was stopped for severe anemia caused by epistaxis . One male 82 years old had SAH in rivaroxaban . Only two patients continued the DOAC with low doses. One patient had brain ischemic attack. 3 pt (2 in apixaban and 1 in rivaroxaban) had acute coronary artery disease with CHADSVASC about 5. No patient was taking dabigatran before acute coronary syndrome. 123 (18%) were lost to follow up, because followed in other centres, or for discontinuation of therapy (poor compliance) or for communication failed. Minor bleeding events were nosebleeds and bleeding gums, and never require to stop therapy.

For control group we utilized the data of our hospital transfusional centre that showed an incidence of bleeding with emergency department access of 1,54 x 100 pts/year in patients in VKA therapy. In our work there were only 6 major bleeding: the date is statistically significant (P < 0,05). Our patients were older than patients followed by transfusional centre (mean age 88 years vs 76 years).



**Figure 1:** Apixaban was the most prescribed drug (34% of patients), followed by dabigatran (33%), rivaroxaban (30,3%) and edoxaban (2,7%).

**Discussion**

The purpose of this work was to assess the safety and efficacy of apixaban, dabigatran, edoxaban and rivaroxaban in the elderly patients with nonvalvular atrial fibrillation. It is a major risk factor for stroke in the elderly population. The use of anticoagulation in patients

with AF greatly reduces the risk for stroke, but results in an increased risk of bleeding. Over the past several years, direct oral anticoagulants (DOACs, dabigatran, rivaroxaban, and apixaban) have been used in place of warfarin for stroke prevention in AF. In our work one patient had an embolic stroke and shift to dabigatran Two patients that assumed dronedarone and were in apixaban therapy, were shifted to edoxaban (when the drug was available) even if there were no complications with the previous drug, but for the minor drug to drug interaction. Bleeding complications remain the major concern for patients receiving DOAC therapy, Overall, GI bleeding was the most commonly recorded major hemorrhage in these patients (2/3 of the total) which is similar to previous reports [16]. In our work, in 3 patients (3/4 patients) the cause of gastrointestinal bleeding was cancer and the forth had inflammatory bowel disease. None patient in our work had intracranic hemorrhage. Our control group is based on transfusional centre patients and the two groups are not totally homogeneous because the mean age of the last one was 78 y while in our group the age was higher. It was impossible to become the two groups homogeneous because we took a preformed group of our transfusional centre. In this group major bleeding occurred in 1,54 x 100 pt./year and this is statistically significant with  $p < 0,05$ . Relative risk in DOAC treatment was about 0,35. Respect on literature, in which there are only few study's about bleeding incidence in VKA treated patients, our transfusional centre's value is lower and so the importance of our results is greater [17]. In this report we analyzed only the patients older than 74 years but our group based on 1014 pt (aged 33 - 98 y) showed that there is a difference between the older and the rest of the group in major bleeding: none younger patient presented clinically relevant hemorrhagic complications and this is statistically significant ( $p < 0,05$ ). No statistical significance resulted between apixaban, rivaroxaban and dabigatran in major bleeding ( $p < 0,1$ ). We find no difference in ACS and VTE between patients older or younger than 75 years. Older group presented more comorbidities as hypertension, renal dysfunction, chronic coronary disease and cardiac failure, in fact thromboembolic risk was greater (4,57 VS 4,0) and also the hemorrhagic risk was greater. CAD was present in 21% of our patients but no patients was in DAPT at the beginning of DOAC therapy [18]. Usually our patients have chronic coronary disease but only 3 patients had coronary acute syndrome, not related to assumed therapy, in fact 2 were in apixan and one was in rivaroxaban. Because at the time of our study in literature hemorrhagic risk in triple association after primary PTCA seemed to be greater with NOAC and there was a lack of conclusive studies [19], our patients in the first six months were treated with VKA, aspirin and clopidogrel and after this period only one returned to low dose apixaban associated only to aspirin, without hemorrhagic complications. More recently, the PIONEER AF-PCI study [20] randomized 2124 patients with non-valvular AF who had undergone PCI with stenting and the primary safety endpoint, consisting of TIMI clinically significant bleeding, was lower in the two groups receiving rivaroxaban than in the group receiving standard therapy with VKA. Also the REDUAL-PCI study [21] investigated use of two different doses of dabigatran, resulting in a risk reduction of bleeding: the difference in risk between the dabigatran 110-mg + P2Y12 inhibitor group and the triple-therapy group (DAPT+ VKA) was 48% and the difference in risk between the 150-mg dual-therapy group and the corresponding triple-therapy group was 28%.

For Edoxaban the number of patients and their follow up is too small. Discontinuation of DOAC therapy was recorded in 8 patients or for acute coronary syndrome or for GI hemorrhage.. In one of these the drug was stopped for reduced compliance. The adherence to the therapy had been good (18% lost). The dose was reduced for dabigatran if the patient was older than 80 years, or renal function was decreased, with calculated creatinine clearance 30 - 50 mL/min. For rivaroxaban the dosage was reduced to 15 mg once a day if calculated creatinine clearance was 15 - 49 mL/min. The low dose of apixaban 2,5 mg twice a day was used if the patient had almost two of these parameters, age major of 80 years, reduced calculated creatinine clearance (15 - 29 ml/m) or body weigh lower than 60 Kg [22]. Therefore it occurred that sometimes other specialists suggested the doac and its dose, so in particular caused that some therapy was lower respect of real need of patients. Apixaban was the most frequent drug under-administered. This fact is very important because the efficacy was reduced also if the safety was better. Fortunately no patients treated with low dose had thrombo-embolic events. In a recent meta-analysis of 71 683 patients they were included in phase 4 three randomized trials compare new anticoagulation with warfarin in preventing stroke and systemic embolism [23].

Like other real life studies we can conclude saying that DOAC are safe and effective also in a group of old patients (mean age 88 y) with more comorbidities, so with more elevated risk score for stroke and bleeding. Because of these real world results, also ESC guidelines

suggest we should prefer a NOAC [24] when anticoagulant is required and evaluate which is the best one for our patient case-by-case. We should also remember to use low dose in particular cases that are not so rare in clinical practice. Physicians and patients must be aware that DOAC are more comfortable and manageable than VKA, because of the lack of need of serial INR test and the lack of food interactions, therefore they have also interactions like all drugs, they need to be tested and monitored to avoid hepatic and renal toxicity that can cause an over effect in anticoagulation. So, we tried to choose the best molecule for every patient, at the light of anamnesis, other pathologies, other drugs, blood exams. Most important interactions to avoid are with gpP and CYP3A4 (this one not for dabigatran) potent inhibitors or inducers, like dronedarone (not interaction with edoxaban), cyclosporin, anti-fungal azoles and we should carefully value dosage of amiodaron, verapamil, chinidin and also avoid drugs with moderate effects on gpP and CYP3A4 if patient has creatinine clearance < 80 ml/min.

### Conclusion

New anticoagulants significantly reduced the risk of stroke compared to warfarin and the benefit was especially linked to the reduction in hemorrhagic strokes. Also there was a reduction in the causes of mortality and intracranial hemorrhage [15]. The conclusions of our dedicated clinic experience are in agreement with the literature: scarce side effects, lower the percentages of major events and low proportion of substitutions/suspension of the therapy. The DOAC dedicated clinic improved compliance, adherence, was liked by patients and doctors, without additional substantial costs for the national health system.

### Conflict of Interest

We declare we have not conflict of interest.

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