# Characteristics of apixaban-treated patients, evaluation of the dose prescribed and the persistence of treatment: a cohort study in Catalonia.

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**Abstract:**

Background: Apixaban is a direct oral anticoagulant, which inhibits the factor Xa. It has demonstrated clinical efficacy in prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and a better safety profile compared with warfarin.

Objectives: (1) To describe the characteristics of non-valvular atrial fibrillation patients beginning treatment with apixaban; (2) to analyse concomitant prescriptions of medications that could potentially interact with apixaban; (3) to evaluate the level of appropriate usage according to the recommended dosage; and (4) to estimate the level of apixaban persistence among naïve and non-naïve patients.

Methods: Cohort study using data from primary care (SIDIAP database, users of the Institut Català de la Salut; Catalonia, Spain) from August 2013 to December 2015.

Results: Mean age for apixaban treated patients was 71.8 years (SD = 11.1) and 55.6% were male. 3.2% of patients receiving apixaban were taking drugs described as potentially related to either pharmacokinetic or pharmacodynamic interactions. According to the summary of product characteristics 81.1% of patients with a recommended dose of 2.5mg b.i.d. and 51.8% with a recommended dose of 5mg b.i.d., actually took this dose. After one year of follow up 62.6% of the apixaban users showed good adherence.

Conclusion: The prescribed dose of apixaban did not fully follow the recommended dose, particularly in patients who were treatment naïve. Patients with a prior history of anticoagulant treatment were more likely to remain persistent to treatment with apixaban.

Key words: apixaban, anticoagulants, drug use review, medication adherence, electronic health records.

## Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia with a current estimated prevalence in the developed world of approximately 1.5–2% of the general population. It can cause symptoms (palpitations, dizziness) but is sometimes asymptomatic (episodes of 'silent' AF). Anticoagulation therapy is critical for reducing the risk of consequences of AF, as patients with AF have a 5-fold risk of stroke and a 3-fold incidence of congestive heart failure, and higher mortality.[1,2] Vitamin K Antagonists (VKAs) significantly reduce the risk of stroke and death in patients with non-valvular AF (NVAF) and have long been the cornerstone of therapy for this condition.[3] From 2011, based upon randomized trials demonstrating their comparable or superior efficacy and safety relative to VKAs, direct oral anticoagulants (DOACs) became available. Unlike VKAs, DOACs do not require laboratory monitoring, do not have a narrow therapeutic index, and have fewer food and drug interactions.[2,4]

Apixaban is one of the novel DOACs that, by inhibiting the factor Xa, has emerged as an alternative to VKAs in the prevention of stroke and systemic embolism (SE) in adult patients with NVAF.[5]

The clinical efficacy of apixaban for prevention of stroke and SE in adult patients with NVAF was demonstrated, as well as an improved safety profile compared with aspirin, in one phase III clinical trial (AVERROES) and these endpoints were compared with warfarin in another phase III clinical trial (ARISTOTLE).[6,7] In Spain the indication of apixaban for the prevention of stroke and SE in patients with NVAF started in August 2013.[8] The Spanish Agency for Medicines and Health Products (AEMPS) recommends DOACs in patients with NVAF and history of haemorrhagic stroke or high risk of intracranial haemorrhage, ischaemic stroke with clinic or neuroimaging of high risk of intracranial haemorrhage, in patients with poor control of INR (international normalized ratio (INR) 2-3, and in patients allergic or intolerant to VKAs.[8]

Since apixaban commercialization was initiated in Spain, little is known about its adoption into daily clinical practice. By way of this real world data drug utilization study, we aim to assess apixaban patients characteristics. The aim of this study was to characterise NVAF patients using apixaban for stroke prevention, as well as to analyse the co-medications prescribed and evaluate the level of appropriate usage according to the dosage recommended in the Summary of Product Characteristics (SmPC) and the adherence and persistence in this treatment.

## Methods

We carried out a non-interventional post authorization study on the use of apixaban in Primary Care Catalonia's (Spain) public health care system. The protocol of the present study has been published elsewhere (http://www.encepp.eu/encepp/openAttachment/fullProtocol/13179;jsessionid=IWKy4mJFYCC1a-TnyRqJJDh1o01ZLKLHOwliAY3aaVa0-Ui4ubQ0!1617953341).

Data were obtained from the Information System for Research in Primary Care (SIDIAP) database which contains anonymized clinical information from 279 primary healthcare (PHC) centres managed by the Catalan Health Institute (ICS), which covers more than 5.8 million patients (approximately 80% of the Catalan population, which represents more than 10% of the Spanish population). This information emerges from ECAP™ (electronic health records in PHC) and it includes socio-demographic characteristics, health conditions registered as ICD10 codes, clinical parameters, toxic habits, laboratory data, and General Practitioners' prescriptions and their corresponding pharmacy invoice data identified through ATC codes.

The study cohort included all eligible subjects from the source population who had a new prescription for apixaban from August 2013 until December 2015 and a previously recorded

diagnostic of NVAF (classified by ICD-10 codes). These subjects were divided in two cohorts: patients who have initiated with apixaban in the period August 2013 to December 2015 as treatment naïve (no prior prescription of VKAs in the 12 months before the index date), and non-naïve, this is, patients who have been previously treated with VKAs or other DOAC (dabigatran or rivaroxaban) in the 12 months before index date.

Apixaban prescriptions were identified through Anatomical Therapeutic Chemical (ATC) codes from ECAP prescriptions.[9] Patients were followed-up until discontinuation of apixaban (patient discontinuation was defined as two or more consecutive months after the las supply).

Data on sex, age, weight, smoking and alcohol habits, MEDEA socioeconomic index[10], estimated glomerular filtration rate, comorbidities (number and type by ICD-10 codes) were collected at the index date. $CHADS_2$, $CHA_2DS_2VASc$ and HAS-BLED score were calculated based on these data.

Data for relevant co-medications were identified and collected from prescriptions at the index date and up to one month after this date.

Data on the dosage and frequency of apixaban, 2.5mg b.i.d and 5 mg b.i.d., were collected from the invoice record. Only data until 30/09/2015 were analysed for this objective, as the system has a two-three months delay to get the invoice data of the prescriptions and for those patients prescribed apixaban after 30/09/2015, data on the dosage would not have been registered.

To assess the adherence in those patients with data of at least one year we used the medication possession ratio (MPR), defined as the ratio of the number of days of medication supplied within the refill interval to the number of days in the refill interval.

Both, adherence and therapeutic persistence to apixaban, was assessed through pharmacy invoice data for patients who initiated treatment between August 2013 and December 2014 (n=1,971), in order to analyse data of at least one year of follow-up after initiation. It was calculated based on the pattern of repeat dispensed prescriptions.

## Statistical analysis

Patient's characteristics were described using frequencies and percentages for categorical variables and mean, standard deviation for continuous variables, as appropriate.

Level of agreement between real and recommended dose according to SmPC was assessed through Cohen's kappa statistic with its 95% Confidence Interval (95%CI). Time to discontinuation was described using Kaplan–Meier curves.

Regarding missing data, no imputations were carried out.

Data analysis was performed using R Statistical Software (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

## Results

A total of 6,135 patients initiated treatment with apixaban from August 2013 to December 2015, with most being naïve to anticoagulant treatment (76.8%).

Among them, there were more women (55.6%). Apixaban non-treatment naïve patients (mean age 78.1 years, SD 8.7) were older than naïve ones (mean age 71.8 years, SD 11.1); had more comorbidities (any, 92.5% vs. 78.4%); more cardiovascular co-medications (95.9% vs. 86.8%); and higher risks of stroke ($CHA_2DS_2VASc$ mean, 4.4 vs. 3.0) and bleeding (HAS-BLED mean, 2.7 vs. 1.7). BMI could not be calculated for more than a quarter of the apixaban patients, however 31.3% of the remaining patients were overweight or obese (BMI ≥ 25). Generally, patients treated with apixaban were non-smokers (66%), with a relatively good renal function (58.8% had over 60mL/min per 1.73$m^2$), and were elderly (67.1% patients were 70 years and older). Table 1.

We found that 5,011 (81.7%) apixaban-treated patients had at least one comorbidity and 1,469 (23.9%) had 3 or more comorbidities. Overall the studied population the most frequent

comorbidities were hypertension (70%) and diabetes mellitus (32.4%). Cancer was the third more frequent comorbidity (25.5%) among the apixaban- naïve patients and heart failure (33.8%) among the non-naïve ones. Table 1.

The mean $CHA_2DS_2VASc$ score was 3.3 (SD = 1.8) and this was lower for the naïve patients (3.0, SD = 1.7) compared to the non-naïve ones (4.4, SD =1.6). The mean HAS-BLED score was 2.0 (SD = 1.1) for all patients, and 1.7 (SD = 1.0) and 2.7 (SD = 1.1) for the naïve and non-naïve cohorts, respectively. Table 2.

With regard to co-prescribed medications in the overall apixaban-treated patient population, 86.1% had cardiovascular medications, 70.2% had proton pump inhibitors, 45.7% had lipid-modifying agents, 22.9% had drugs used in diabetes management and 22.2% had antidepressants. Almost all patients taking apixaban had other medication prescribed concomitantly. Drugs described in the SmPC as potentially having a pharmacokinetic interaction with apixaban were prescribed in 4.3% of patients, and drugs described as potentially having a pharmacodynamic interaction were prescribed in 68.4% of patients. Table 3.

We analysed which patients received the recommended dose according to the SmPC, however there was an elevated number of missing data [39.7% (n=2,043) by the dispensed dose and 18.2% (n=935) by the recommended dose] which complicated a proper assessment of this objective.

Therefore, we only had complete data to achieve this objective in 2,546 patients (49.5%). Among patients with recommendation for dose reduction (n = 360, 14.1%), a relatively low number of patients (n=68, 2.7%) had 5mg b.i.d. dose prescribed. Among those ones with recommendation for the standard 5mg b.i.d. dose (n=2,186, 85.9%), 41.4% (n=1,053) had the 2.5mg b.i.d. dose prescribed, despite not having met all the necessary criteria for this dose reduction. This dosing pattern was more commonly associated to treatment naïve patients (n=815, 51.7%) compared to

non-treatment naïve patients (n=238, 24.8%). See Tables 4a and 4b for use of apixaban according to dose prescribed for naïve and non-naïve patients.

For the 854 patients (43.3%) not discontinuing the medication and having at least one year of follow-up to calculate adherence, 62.6% of them showed good adherence (MPR between 80 % and 120%). Regarding persistence, there were 652 patients (33.1%) discontinuing treatment in the first month (Table 5).

After one month of treatment initiation, almost half of the treatment naïve patients (45.7%, n= 596) discontinued treatment versus less than 10% of the non-naïve patients (8.4%, n= 56). Table 5. When analysing the characteristics among treatment naïve patients who discontinued after the first month of treatment versus treatment naïve patients who were persistent for one year, there were more women (66.9% vs 46.2%, difference: 10.7%, 95%CI from 4.3% to 17.0), who were younger [66.3 years old (±13.3) vs 74.6 years old (±10.5), mean difference: 7.6, 95% CI: 6.2 from to 9.0] and had lower risk scores for stroke [In $CHA_2DS_2VASc$ 2.4 (±1.6) vs 3.7 (±1.7), mean difference: 1.3, 95% CI: 1.1 from to 1.5] and bleeding [In HAS-BLED 1.4 (±0.9) vs 2.1 (±1.0), mean difference: 0.7, 95% CI: 0.6 from to 0.8].

## Discussion

During the study period, a total of 6,135 patients with NVAF met inclusion criteria for this cohort study, of which 1,423 patients (23.2%) were non-naïve to oral anticoagulation treatment. We found more women than men were treated with apixaban, with a mean age of 73.2 years. Two studies carried out in USA had a similar median ages as that reported in this study (73 and 70.9 respectively) but a higher proportion of men being treated with apixaban (53.1% and 59.7%).[11,12]

Our results showed that 1,469 patients (23.9%) had 3 or more associated comorbidities, with

hypertension present in 70.0% of them, while US-based studies report more than 85% of the apixaban-treated patients had hypertension.[11,12] For diabetes mellitus our results were similar (32.4% vs 25-35%% of the patients analysed in the US-based studies) but in the case of the ischemic heart disease, only 13.1% of our patients who started apixaban had coronary artery disease vs 30% of patients in the Desai et al. study.[11–13] It is important to note that in their study, only 20 patients initiated apixaban treatment but in patients who started other DOACs (rivaroxaban, dabigatran) higher rates of ischemic heart disease were also observed (30% from 821 patients and 28% from 1,982 patients under treatment with rivaroxaban and dabigatran respectively). In the Yao et al. study, the proportion of apixaban-treated patients with vascular disease was 28.3% (n=7695)[11], while in the Li et al. study they reported only 8.9% (n=38470) of patients with myocardial infarction.[12]

In our study, the mean $CHADS_2$ score was not different from that in the ARISTOTLE trial or the the Li et al. study (2.0 ± 1.4 vs 2.1 ± 1.1 and 2.1±1.3 respectively) .[7,12] In the Desai study, patients starting treatment with apixaban had a $CHA_2DS_2VASc$ mean score of 2.05 (± 0.94) while patients in our study had had a higher $CHA_2DS_2VASc$ mean score of 3.3 (± 1.8), similar to the one of the Li et al. study (3.2±1.8) but not as high as that in Yao et al. (4 ±1) .[11–13]

With regard to bleeding risk, our patients' mean HAS-BLED score was higher (2.0 ± 1.1) than for the patients in the Desai et al. cohort (1.60 ± 0.82) but the same as in the Yao et al. study.[11,13] This higher mean of HAS-BLED score could be partly explained by the incorrect dose prescription according to the SmPC as trying to minimise the risk of bleeding by dose reduction even not meeting all the criteria. In our population, treatment naïve patients had lower HAS-BLED scores than non-treatment naïve patients, however the proportion of patients in the treatment-naïve cohort receiving low-dose of apixaban was even higher.

The efficacy and safety of the DOACs might be compromised by co-administration of other drugs

[14,15] and dose adjustment may be needed when using certain DOACs concomitantly with other drugs.[16]

In this study 86.1% of apixaban- treated patients were taking cardiovascular drugs. Diltiazem has been described as a drug with interaction potential and it was prescribed to a 3.8% (n=236) of the patients of our study. However, the apixaban SmPC does not recommend a dose adjustment with drugs that are weak to moderate CYP3A4 or P-gp inhibitors. In the ARISTOTLE trial 30.1% of patients received a calcium channel blocker as a prescribed co-medication.[7]

With regard to the potential pharmacodynamic interaction with NSAIDs, the apixaban SmPC warns of its use concomitant with NSAIDs, though 29.4% (N= 1,805) of our studied patients used both drugs. A previous study has reported an increase of apixaban exposure because of augmented bioavailability when administer concomitantly with naproxen[17] It is well known that anticoagulants may increase the risk of haemorrhage, including GI haemorrhage, especially with NSAIDs with a long half-life. However, apixaban has shown lower GI bleeding rates in comparison with VKA and also with other DOACs.[7,11,12] In our study 16.1% (n= 985) in the overall population had a platelet aggregation inhibitor co-prescribed in 18.2% of treatment naïve patients and 9.1% of non-treatment naïve patients, which is consistent with the number of patients with CAD (coronary artery disease). Table 3.

Close monitoring for signs of bleeding is recommended when an anticoagulant is being used with other platelet aggregation inhibitors, especially when dual antiplatelet therapy is going to be considered, as it has been described as increasing the risk of major haemorrhagic complications in patients treated after and acute coronary syndrome.[16,18,19] Recent ESC guidelines on dual antiplatelet treatment (DAPT) in CAD recommends, in patients receiving oral anticoagulation concomitantly, to shorten the DAPT as much as possible as well as discontinuation of antiplatelet treatment at 12 months.[20]

When a new drug enters the market, and in particular, a DOAC, physicians could prescribe lower doses because its particular drug profiles, characteristics and different dosages, and also patients comorbidities.[21–23] When we analysed the first doses of apixaban prescribed at baseline, non-naïve patients had better rates of correct dosage, though in both groups when the initial recommended dose was 5 mg b.i.d. it was correctly prescribed to only around half the patients (42.6% in the naïve group and 68.9% in the non-naïve group).[24]

Therapeutic adherence was assessed through pharmacy invoice data for patients initiating treatment in 2013 and 2014 (n=1,971). Among these patients, therapeutic adherence was measured in 43.3% of the apixaban cohort (n=854) that had at least one year of follow-up, representing 32.5% of the naïve and 64.6% of the non-naïve population. The adherence was considered good in 61.1% of the naïve and 64.2% of the non-naïve patients. In one US-based study, Yao et al. found a similar result with 61.9% apixaban adherence (PDC≥80%) within 6 months of follow up, with apixaban demonstrating the highest adherence rates among the DOAC studied.[25] We used the threshold of 80% MPR for good adherence as defined in the literature but we also wanted to see the percentage over 120% as it could be a limitation of the MPR formula used to calculate it. [26]

Persistence at one year was 43.3% for the whole cohort and was being higher for the non-naïve patients (64.6%). The overall discontinuation rate for the first month was 33.1%, which was higher than those observed during the same time period in clinical trials (30). The discontinuation rate for apixaban in the phase III clinical trial was 25.3% vs 27.5% for warfarin.[7] There is not a clear explanation for this finding and this study cannot help in providing potential reasons for it though similar patterns have been observed in other DOAC studies.[27]

The rate of persistence in our study, 43.3%, is much lower than that from a population cohort study from the Stockholm region, which was 85.9% after 1 year.[28] Similarly, in another study

performed in general practices in the UK using the CPRD database, treatment persistence with apixaban was also higher, reaching 82.8% at 12 months.[29] When compared to warfarin, patients treated with DOACs generally tend to demonstrate better persistence, although more studies on this topic should be performed.[30]

Our results showed that non-naïve patients, who mostly received VKA before starting a DOAC, have better treatment persistence than naïve patients. This finding suggests that anticoagulant-experienced patients may be more aware of the importance of treatment adherence and , if they were persistent with VKA, which require a frequent INR monitoring, they would be persistent with a "less strict" anticoagulant treatment follow-up as it has also been reported recently in an USA study[31]. It also raised an important issue as a poor adherence even persistence to anticoagulant treatment in patients with NAVF would be translated into higher stroke risk[32].

We also think that future interventions on patient education for long therapies on asymptomatic diseases, as DOAC for stroke prevention in patients with NVAF, will have to be developed, especially in naïve patients as the under use/under dose .

**Strengths and Limitations**

The strengths of our study are representativeness for the general population, with a database that covers almost the 80% of the Catalonian population, with complete socio-demographic and health records, long follow-up, and real clinical practice data.

Some specific limitations in our database are the lack of association between GP's prescriptions and dispensing associated to these prescriptions, and the high number of missing values of the first dose prescribed.

We do not have access to electronic health records from the hospitals and some first prescriptions of DOAC are filled by specialist physicians from the hospitals (mainly Cardiologists).

One specific limitation of the current study is that the HAS-BLED score might be underestimated as we equal the result for the item "Labile INR" to score 0, when no INR was registered.

In Spain, DOAC are less frequently prescribed than in the rest of European countries due to the more restrictive recommendations for their use stablished by the AEMPS.[8]

Because the high percentage of discontinuation rates we are now studying the discontinuation rates in the rest of DOAC, and comparing them with VKA.

This study has missing data from pharmacy claims and for some variables as it is common in observational studies using electronic databases (information bias). According to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) we have reported the missing data and as we were not making any association we have just handled with these data by reporting them without performing any statistical inference.[33]

## Conclusion

Almost all the patients treated with apixaban had at least one comorbidity. Patients who were treatment naïve had lower risks of stroke and bleeding than patients who were not treatment naïve. In the patient population assessed, less than 5% of patients were concurrently receiving a medicine potentially associated with a pharmacokinetic drug interaction. The prescribed dose of apixaban did not fully follow the recommended dose, particularly in patients who were treatment naïve. Patients with a prior history of taking oral anticoagulants were more likely to remain persistent to treatment with apixaban.

## Ethic Statement

The study protocol was approved by the Ethics Committee of the "IDIAP Jordi Gol" and classified by the Spanish Agency of Pharmacy and Medical Products (AEMPS). No inform consents were compile from the patients as the characteristics of the study did not required it.

## Conflict of interest

All the authors declare no conflict of interest.

Data can be accessed through request to the corresponding author.

## References


1. Kirchhof P, Curtis AB, Skanes AC, Gillis AM, Samuel Wann L, John Camm A. Atrial fibrillation guidelines across the Atlantic: a comparison of the current recommendations of the European Society of Cardiology/European Heart Rhythm Association/European Association of Cardiothoracic Surgeons, the American College of Cardiology Fou. *Eur Heart J*. 2013;34(20):1471-1474. doi:10.1093/eurheartj/ehs446
2. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33(21):2719-2747. doi:10.1093/eurheartj/ehs253
3. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288(19):2441-2448. http://www.ncbi.nlm.nih.gov/pubmed/12435257.
4. Nunes JPL, Rodrigues RP, Gonçalves FR. Comparative analysis and meta-analysis of major clinical trials with oral factor Xa inhibitors versus warfarin in atrial fibrillation. *Open Hear*. 2014;1(1):e000080. doi:10.1136/openhrt-2014-000080

5. Hanna MS, Mohan P, Knabb R, Gupta E, Frost C, Lawrence JH. Development of apixaban: a novel anticoagulant for prevention of stroke in patients with atrial fibrillation. *Ann N Y Acad Sci*. 2014;1329:93-106. doi:10.1111/nyas.12567

6. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-817. doi:10.1056/NEJMoa1007432

7. Granger CB, Alexander JH, McMurray JJ V, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039

8. Agencia Española de Medicamentos y Productos Sanitarios. AEMPS. *AEMPS. Criterios Y Recomendaciones Generales Para El Uso de Nuevos Anticoagulantes Orales En La Prevención Del Ictus Y La Embolia Sistémica En Pacientes Con Fibrilación Auricular No Valvular.*; 2012.

9. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC Classification and DDD Assignment.* 16th ed.; 2013. https://www.whocc.no/filearchive/publications/1_2013guidelines.pdf.

10. Domínguez-Berjón MF, Borrell C, Cano-Serral G, et al. [Constructing a deprivation index based on census data in large Spanish cities(the MEDEA project)]. *Gac Sanit*. 22(3):179-187. http://www.ncbi.nlm.nih.gov/pubmed/18579042.

11. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. *J Am Heart Assoc*. 2016;5(6). doi:10.1161/JAHA.116.003725

12. Li X, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus

warfarin in non-valvular atrial fibrillation patients in “real-world” clinical practice. *Thromb Haemost*. 2017;117(6):1072-1082. doi:10.1160/TH17-01-0068

13. Desai NR, Krumme AA, Schneeweiss S, et al. Patterns of initiation of oral anticoagulants in patients with atrial fibrillation- quality and cost implications. *Am J Med*. 2014;127(11):1075-82.e1. doi:10.1016/j.amjmed.2014.05.013
14. Di Minno A, Frigerio B, Spadarella G, et al. Old and new oral anticoagulants: Food, herbal medicines and drug interactions. *Blood Rev*. February 2017. doi:10.1016/j.blre.2017.02.001
15. Cascorbi I. Drug interactions--principles, examples and clinical consequences. *Dtsch Arztebl Int*. 2012;109(33-34):546-55; quiz 556. doi:10.3238/arztebl.2012.0546
16. APPRAISE Steering Committee and Investigators, Alexander JH, Becker RC, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. *Circulation*. 2009;119(22):2877-2885. doi:10.1161/CIRCULATIONAHA.108.832139
17. Frost C, Shenker A, Gandhi MD, et al. Evaluation of the effect of naproxen on the pharmacokinetics and pharmacodynamics of apixaban. *Br J Clin Pharmacol*. 2014;78(4):877-885. doi:10.1111/bcp.12393
18. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. *J Thromb Thrombolysis*. 2011;31(3):326-343. doi:10.1007/s11239-011-0561-1
19. Gorczyca-Michta I, Wożakowska-Kapłon B. New oral anticoagulants - will they be

used with antiplatelet drugs in patients with atrial fibrillation after acute coronary syndrome? *Postep w Kardiol interwencyjnej = Adv Interv Cardiol*. 2013;9(4):348-352. doi:10.5114/pwki.2013.38864

20. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J*. August 2017. doi:10.1093/eurheartj/ehx419
21. Viprey M, Jeannin R, Piriou V, et al. Prevalence of drug-related problems associated with direct oral anticoagulants in hospitalized patients: a multicenter, cross-sectional study. *J Clin Pharm Ther*. 2017;42(1):58-63. doi:10.1111/jcpt.12473
22. McCormack JP, Allan GM, Virani AS. Is bigger better? An argument for very low starting doses. *Can Med Assoc J*. 2011;183(1):65-69. doi:10.1503/cmaj.091481
23. Savarese G, Sartipy U, Friberg L, Dahlström U, Lund LH. Reasons for and consequences of oral anticoagulant underuse in atrial fibrillation with heart failure. *Heart*. January 2018:heartjnl-2017-312720. doi:10.1136/heartjnl-2017-312720
24. Troncoso A, Diogène E. Dabigatran and rivaroxaban prescription for atrial fibrillation in Catalonia, Spain: the need to manage the introduction of new drugs. *Eur J Clin Pharmacol*. 2014;70(2):249-250. doi:10.1007/s00228-013-1593-6
25. Yao X, Abraham NS, Alexander GC, et al. Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation. *J Am Heart Assoc*. 2016;5(2):e003074. doi:10.1161/JAHA.115.003074
26. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of Adherence in Pharmacy Administrative Databases: A Proposal for Standard Definitions and

Preferred Measures. *Ann Pharmacother*. 2006;40(7-8):1280-1288. doi:10.1345/aph.1H018

27. Manzoor BS, Lee TA, Sharp LK, Walton SM, Galanter WL, Nutescu EA. Real-World Adherence and Persistence with Direct Oral Anticoagulants in Adults with Atrial Fibrillation. *Pharmacother J Hum Pharmacol Drug Ther*. July 2017. doi:10.1002/phar.1989

28. Forslund T, Wettermark B, Hjemdahl P. Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation. *Eur J Clin Pharmacol*. 2016;72(3):329-338. doi:10.1007/s00228-015-1983-z

29. Johnson ME, Lefèvre C, Collings S-L, et al. Early real-world evidence of persistence on oral anticoagulants for stroke prevention in non-valvular atrial fibrillation: a cohort study in UK primary care. *BMJ Open*. 2016;6(9):e011471. doi:10.1136/bmjopen-2016-011471

30. Obamiro KO, Chalmers L, Bereznicki LRE. A Summary of the Literature Evaluating Adherence and Persistence with Oral Anticoagulants in Atrial Fibrillation. *Am J Cardiovasc Drugs*. 2016;16(5):349-363. doi:10.1007/s40256-016-0171-6

31. McHorney CA, Crivera C, Laliberté F, Germain G, Wynant W, Lefebvre P. Adherence to rivaroxaban versus apixaban among patients with non-valvular atrial fibrillation: Analysis of overall population and subgroups of prior oral anticoagulant users. ten Cate H, ed. *PLoS One*. 2018;13(4):e0194099. doi:10.1371/journal.pone.0194099

32. Raparelli V, Proietti M, Cangemi R, Lip GYH, Lane DA, Basili S. Adherence to oral anticoagulant therapy in patients with atrial fibrillation. *Thromb Haemost*.

2017;117(2):209-218. doi:10.1160/TH16-10-0757

33. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS medicine. doi:10.1371/journal.pmed.1001885

# TABLES

**Table 1**. Sociodemographic characteristics, comorbidities, risk of stroke and haemorrhage of patients treated with apixaban.

| **Categorical** | **N= 6,135** | **Naïve (n=4,712, 76.8%)** | **Non-naïve (n=1,423, 23.2%)** |
|---|---|---|---|
| **Sex** | | | |
| Female | 3,412 (55.6%) | 2,661 (56.5%) | 751 (52.8%) |
| Male | 2,723 (44.4%) | 2,051 (43.5%) | 672 (47.2%) |
| **Age (years)** | | | |
| **Mean (SD)** | 73.2 (11.0) | 71.8 (11.1) | 78.1 (8.7) |
| ≥80 | 1,879 (30.6%) | 1,148 (24.4%) | 731 (51.4%) |
| **BMI (kg/m$^2$)** | | | |
| Missing | 1,685 (27.5%) | 1,424 (30.2%) | 261 (18.3%) |
| 18.5-25 (Normal) | 676 (11.0%) | 423 (9.0%) | 253 (17.8%) |
| <18.5 (Underweight) | 18 (0.3%) | 12 (0.3%) | 6 (0.4%) |
| 25-30 (Overweight) | 1,722 (28.1%) | 1,229 (26.1%) | 493 (34.6%) |
| >30 (Obese) | 2,034 (33.2%) | 1,624 (34.5%) | 410 (28.8%) |
| **Glomerular Filtration Rate (mL/min/1.73 m$^2$)** | | | |
| Missing | 1,249 (20.4%) | 1,030 (21.9%) | 219 (15.4%) |
| ≥ 60 | 3,605 (58.8%) | 2,873 (61.0%) | 732 (51.4%) |
| 45 - 59 | 798 (13.0%) | 537 (11.4%) | 261 (18.3%) |
| 30 - 44 | 400 (6.5%) | 228 (4.8%) | 172 (12.1%) |
| < 30 | 83 (1.4%) | 44 (0.9%) | 39 (2.7%) |
| **Comorbidities** | | | |
| **Comorbidities (n)** | | | |
| ≥ 3 | 1,469 (23.9%) | 854 (18.1%) | 615 (43.2%) |
| **Comorbidity type** | | | |
| Heart failure | 866 (14.1%) | 385 (8.2%) | 481 (33.8%) |
| Peripheral artery disease | 323 (5.3%) | 189 (4.0%) | 134 (9.4%) |

| | | | |
|---|---|---|---|
| Ischemic heart disease | 802 (13.1%) | 460 (9.8%) | 342 (24.0%) |
| Acute myocardial | 246 (4.0%) | 140 (3.0%) | 106 (7.4%) |
| Hypertension | 4,295 (70.0%) | 3,172 (67.3%) | 1,123 (78.9%) |
| Diabetes mellitus | 1,986 (32.4%) | 1,404 (29.8%) | 582 (40.9%) |
| Deep vein thrombosis and pulmonary embolism | 83 (1.4%) | 45 (1.0%) | 38 (2.7%) |
| Liver disease | 348 (5.7%) | 270 (5.7%) | 78 (5.5%) |
| Renal disease | 927 (15.1%) | 562 (11.9%) | 365 (25.7%) |
| Cerebrovascular disease | 891 (14.5%) | 490 (10.4%) | 401 (28.2%) |
| Cancer | 1,606 (26.2%) | 1,202 (25.5%) | 404 (28.4%) |
| Chronic obstructive pulmonary | 1,206 (19.7%) | 839 (17.8%) | 367 (25.8%) |

Table 2. Risk score for stroke and haemorrhage

| **Risk of stroke and haemorrhage** | **N= 6,135** | **Naïve (n=4,712, 76.8%)** | **Non-naïve (n=1,423, 23.2%)** |
|---|---|---|---|
| **$CHADS_2$** | | | |
| 0 | 880 (14.3%) | 831 (17.6%) | 49 (3.4%) |
| 1 | 1,609 (26.2%) | 1,426 (30.3%) | 183 (12.9%) |
| ≥2 | 3646(59.4%) | 2455 (52.1%) | 1191 (83.7%) |
| **$CHA_2DS_2VASc$** | | | |
| Missing | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 0 or 1 (women) | 480 (7.8%) | 457 (9.7%) | 23 (1.6%) |
| 1 (not women) | 375 (6.1%) | 344 (7.3%) | 31 (2.2%) |
| 2 | 993 (16.2%) | 877 (18.6%) | 116 (8.2%) |
| ≥3 | 4,287 (69.9%) | 3,034 (64.3%) | 1253 (88.1%) |
| **HAS - BLED** | | | |
| Missing | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 0 | 540 (8.8%) | 519 (11.0%) | 21 (1.5%) |
| 1-2 | 3,927 (64%) | 3,317 (70.4%) | 610 (42.9%) |
| ≥3 | 1,668 (27.3%) | 8,76 (18.3%) | 792(55.7%) |

**Table 3**. Potentially interacting medication with apixaban in all apixaban treated patients, in naïve and non-naïve patients.

| Interacting drugs | All (n = 6,135) | Naïve patients (n = 4,712) | Non naïve patients (n = 1,423) |
|---|---|---|---|
| **Any co-medication** | 6,118 (99.7%) | 4.712 (100%) | 1,406 (98.8%) |
| **Pharmacokinetic Interaction** | 261 (4.3%) | 140 (3.0%) | 121 (8.5%) |
| **Antiepileptic** | 16 (0.3%) | 8 (0.2%) | 8 (0.6%) |
| Carbamazepine | 10 (0.2%) | 6 (0.1%) | 4 (0.3%) |
| Phenytoin | 8 (0.1%) | 4 (0.1%) | 4 (0.3%) |
| **Antimycobacterials: rifampin** | 8 (0.1%) | 7 (0.1%) | 1 (0.1%) |
| **Antimycotics: itraconazole** | 1 (0.0%) | 1 (0.0%) | 0 (0.0%) |
| **Antipsychotics: pimozide** | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Calcium channel blockers: diltiazem** | 236 (3.8%) | 124 (2.6%) | 112 (7.9%) |
| **Macrolide antibiotics** | 1 (0.0%) | 0 (0.0%) | 1 (0.1%) |
| **Pharmacodynamical Interaction** | 4199 (68.4%) | 3753 (61.2%) | 446 (7.3%) |
| **Platelet aggregation inhibitors** | 985 (16.1%) | 856 (18.2%) | 129 (9.1%) |
| Clopidogrel | 107 (1.7%) | 88 (1.9%) | 19 (1.3%) |
| Acetylsalicylic acid | 889 (14.5%) | 773 (16.4%) | 116 (8.2%) |
| Other platelet aggregation inhibitors | 18 (0.3%) | 17 (0.4%) | 1 (0.1%) |
| **Heparins** | 161 (2.6%) | 113 (2.4%) | 48 (3.4%) |
| **Systemic corticosteroids** | 234 (3.8%) | 171 (3.6%) | 63 (4.4%) |
| **Non-steroidal anti-inflammatory drugs** | 1,805 (29.4%) | 1,735 (36.8%) | 70 (4.9%) |

**Tables 4**. Use of apixaban according to dose prescribed for patients with available data in naïve (a) and in non-naïve patients (b).

| Recommended dose[b] / Prescribed dose[a] | Missing | 2.5 mg | 5.0 mg | Total | Kappa[1] (95%CI) | p-value[2] |
|---|---|---|---|---|---|---|
| **Missing** | 355 (46.2) | 60 (26.5) | 1,509 (51.5) | **1,924 (49.0)** | **0.07 (0.05 , 0.10)** | <0.001 |
| **2.5 mg** | 232 (30.2) | 132 (58.4) | 815 (27.8) | **1,179 (30.0)** | | |
| **5.0 mg** | 182 (23.7) | 34 (15.0) | 605 (20.7) | **821 (20.9)** | | |
| **Total*** | **769 (100.0)** | **226 (100.0)** | **2,929 (100.0)** | **3,924 (100.0)** | | |

Table 4a. Use of apixaban according to dose prescribed in naïve patients (n=3,924*)

| Recommended dose[b] / Prescribed dose[a] | Missing | 2.5 mg | 5.0 mg | Total | Kappa[1] (95%CI) | p-value[2] |
|---|---|---|---|---|---|---|
| **Missing** | 23 (13.9) | 18 (8.5) | 78 (9.2) | **119 (9.7)** | **0.37 (0.31 , 0.43)** | <0.001 |
| **2.5 mg** | 66 (39.8) | 160 (75.5) | 238 (28.2) | **464 (38.0)** | | |
| **5.0 mg** | 77 (46.4) | 34 (16.0) | 528 (62.6) | **639 (52.3)** | | |
| **Total*** | **166 (100.0)** | **212 (100.0)** | **844 (100.0)** | **1,222 (100.0)** | | |

Table 4b. Use of apixaban according to dose prescribed in non-naïve patients (n=1,222*)

[a] Prescribed dose of Apixaban at start date

[b] Recommended dose was 2.5 if one of the following criteria were met at start date: (1) Two of these three conditions: a) Serum creatinine ≥ 1.5 mg/dL; b) age ≥ 80 and c) body weight ≤ 60 kg or (2) severe renal impairment (creatinine clearance below 30 mL/min)

*Patients with first prescription after 30/09/2015 were excluded

[1]Cohen's Kappa.

[2]p-value for Cohen's Kappa

**Table 5**. **Descriptive of medication adherence and discontinuation rates in patients treated with apixaban**

| Categorical | N=1,971 | Naïve (n=1,305) | Non-naïve (n=666) |
|---|---|---|---|
| **MPR* (categorized)** | | | |
| Less than one year of follow-up | 1,117 (56.7%) | 881 (67.5%) | 236 (35.4%) |
| N (at least 1 year of follow-up) | 854 (43.3%) | 424 (32.5%) | 430 (64.6%) |
| Poor adherence (less than 80%) | 313 (36.7%) | 162 (38.2%) | 151 (35.1%) |
| Good adherence (between 80% and 120%) | 535 (62.6%) | 259 (61.1%) | 276 (64.2%) |
| Over adherence (greater than 120%) | 6 (0.7%) | 3 (0.7%) | 3 (0.7%) |
| **Monthly discontinuation (first year)** | | | |
| 1st Month | 652 (33.1%) | 596 (45.7%) | 56 (8.4%) |
| 2nd-6th Months | 249 (12.6%) | 167(12.8%) | 82(12.3%) |
| 7th-12th Months | 216(10.9%) | 118(9.0%) | 98(14.7%) |

*MPR, medication possession ratio.